

Survival of patients with type 1 diabetes on renal replacement therapy

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ABSTRACT

Patients with type 1 diabetes complicated by end-stage renal disease (ESRD) have an 18 to 30-fold higher standardized mortality-ratio compared to the general population. Comorbidities are more common and survival is worse among patients with diabetes on renal replacement therapy (RRT) compared to other RRT patients. Risks of ESRD and premature death among patients with type 1 diabetes have declined over the past decades. Yet, knowledge on factors affecting the improved prognosis and survival on RRT among patients with type 1 diabetes are limited. Our aim was to investigate whether survival of these patients has improved over time and how comorbidities, biochemical variables, and medication associate with mortality.

Incident cohorts were studied here, including all patients with type 1 diabetes starting chronic RRT in Finland during the study periods. All data came from the Finnish Registry for Kidney Diseases, and information on medication was obtained from the FinDM diabetes database combining data from several Finnish registers including the Finnish Prescription Register. Patients were followed until death or end of follow-up. The main outcome measures were survival probability and relative risk of death according to observed factors. The survival of patients with type 1 diabetes on RRT changed between 1980 and 2005, and comorbidities (coronary artery disease, peripheral artery disease, heart failure, left ventricular hypertrophy, and cerebrovascular disease), biochemical variables (creatinine, albumin, urea, ionized calcium, phosphorus, hemoglobin, C-reactive protein, total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, triglycerides, and HbA1c), and use of medication (angiotensin-converting enzyme inhibitors, angiotensin reseptor blockers, calcium channel blockers, beta-blockers, statins, vitamin D, erythropoiesis-stimulating agents, and phosphate binders) associate with survival. Survival was assessed by Kaplan-Meier curves and relative risk of death by Cox proportional hazards regression.

Median survival time of patients with type 1 diabetes on RRT increased continuously from 3.60 years during 1980–1984 to more than 8 years in 2000–2005 and adjusted relative risk of death decreased 77% respectively. In unadjusted analyses, all monitored comorbidities at the start of RRT were significant predictors of mortality, and when analyzed in a multivariate model, peripheral artery disease (RR 1.9, 95% CI 1.3–2.8), left ventricular hypertrophy (RR 1.7, 95% CI 1.2–2.4), and heart failure (RR 2.5, 95% CI 1.3–4.6) were all independent risk

factors of death. Analyses indicated that one third of deaths in the study population could be attributed to comorbidities. Lower serum creatinine and albumin, and elevated C-reactive protein, were predictors of mortality when measured before RRT start and adjusted for potential confounders. The use of medication was abundant and became more frequent when chronic kidney disease proceeded. Over two thirds of the patients used calcium channel blockers and beta-blockers before entering RRT. After adjustment for age and sex, lower relative risk of death was associated with utilization of calcium channel blockers (RR 0.71, 95% CI 0.53–0.95) and vitamin D (RR 0.70, 95% CI 0.52–0.94) before RRT start. However, when adjusted further with comorbidities, BMI, and serum albumin, no significant association was evident with the use of any medication or mortality.

In conclusion, the survival of patients with type 1 diabetes on RRT has improved over the past decades, and these patients have abundant comorbidity and medication. The results of this study indicate that it might be possible to improve survival further by prevention, early diagnosis, and treatment of comorbidities, treatment of malnutrition, proteinuria, hyperglycemia, chronic inflammation, and efficient RRT. Use of medication seems to keep survival of patients on an equal level to patients that don't require the same medication. Randomized trials are needed in the future to confirm these findings.

ABSTRACT IN FINNISH

Tyypin 1 diabetesta sairastavilla potilailla, joiden diabeettinen munuaistauti on edennyt uremian aktiivihoidon (dialyysihoito tai munuaisensiirto) vaativaksi loppuvaiheen munuaisten vajaatoiminnaksi, on 18–30 -kertainen kuolemanriski muuhun väestöön verrattuna. Uremian aktiivihoidossa olevilla diabeetikoilla on enemmän muita sairauksia ja suurempi kuolemanriski kuin muilla uremian aktiivihoidossa olevilla potilailla. Viime vuosikymmeninä loppuvaiheen munuaisten vajaatoiminnan ja ennen aikaisen kuoleman riski on pienentynyt tyypin 1 diabeetikoilla. Kuolemanriskiin ja parantuneeseen ennusteeseen vaikuttavista tekijöistä uremian aktiivihoidossa olevilla tyypin 1 diabeetikoilla on kuitenkin vain vähän tutkimustietoa. Väitöskirjatutkimuksen tavoitteena oli selvittää, miten eloonjäämisennuste on muuttunut ja miten liitännäissairaudet, biokemialliset muuttujat ja lääkitys vaikuttavat siihen.

Valitsimme tutkimukseen kaikki tutkimusaikana kroonisen uremian aktiivihoidon Suomessa aloittaneet potilaat, joiden munuaistaudin aiheuttajana oli tyypin 1 diabetes. Tiedot potilaista saimme Suomen munuaistautirekisteristä. Potilaiden käyttämä lääkitys selvitettiin FinDM-tutkimuksen tietokannasta, jonka tiedot lääkitymisen osalta tulevat Kansaneläkelaitoksen lääkekorvaustietokannasta. Potilaita seurattiin kuolemaan tai seuranta-ajan päättymiseen saakka. Tutkimme, kuinka näiden potilaiden eloonjäämisennuste on muuttunut vuosina 1980–2005, miten liitännäissairaudet (sepelvaltimotauti, ahtauttava valtimonkoveutauti, sydämen vajaatoiminta, sydämen vasemman kammion hypertrofia ja aivoverenkiertohäiriö), biokemialliset muuttujat (kreatiniini, albumiini, urea, kalsium, fosfori, hemoglobiini, CRP, kokonaiskolesteroli, LDL-kolesteroli, HDL-kolesteroli, triglyseridit ja HbA1c) ja lääkitys (ACE-estäjät, angiotensiinireseptorin salpaajat, kalsiumkanavan salpaajat, beetasalpaajat, statiinit, D vitamiini, erytropoietiini johdoksineen ja fosfaatin sitoajat) vaikuttavat eloonjäämisennusteeseen. Tilastollisessa analyysissä käytettiin Kaplan-Meier -käyriä eloonjäämisennusteen laskemiseen ja Coxin regressioanalyysia suhteellisen kuolemanriskin laskemiseen.

Osoitimme, että verrattaessa vuosina 1980–1984 ja 2000–2005 uremian aktiivihoidon aloittaneita tyypin 1 diabeetikoita, eloonjäämisennuste parani 3,6 vuodesta yli 8 vuoteen ja suhteellinen kuolemanriski aleni 77% myöhäisemmässä ryhmässä. Kaikki munuaiskorvaushoidon alkaessa raportoidut liitännäissairaudet lisäsivät kuolemanriskiä, ja

näistä monimuuttujamallissa analysoituna itsenäisiä kuolemanriskiä lisääviä tekijöitä olivat ahtauttava valtimonkovetustauti (suhteellinen riski 1,9, LV 1,3–2,8), sydämen vasemman kammion hypertrofia (suhteellinen riski 1,7, LV 1,2–2,4) ja sydämen vajaatoiminta (suhteellinen riski 2,5, LV 1,3–4,6). Kolmasosan kuolemista voidaan arvioida aiheutuneen raportoiduista liitännäissairauksista. Ennen uremian aktiivihoidon aloittamista mitattu matalampi seerumin kreatiniini ja albumiini sekä kohonnut CRP liittyivät lisääntyneeseen kuolemanriskiin myös sekoittavilla tekijöillä vakioinnin jälkeen. Lääkityksen käyttö oli yleistä näillä potilailla ja lisääntyi munuaistaudin edetessä. Yli kaksi kolmasosaa potilaista käytti kalsiumkanavan salpaajia ja beetasalpaajia ennen uremian aktiivihoidon aloitusta. Kalsiumkanavan salpaajien (suhteellinen riski 0,71, LV 0,53–0,95) ja D vitamiinin (suhteellinen riski 0,70, LV 0,52–0,94) käyttöön liittyi pienempi kuolemanriski ikä- ja sukupuolivakioinnin jälkeen, mutta vakiointi muilla sekoittavilla tekijöillä hävitti tämän yhteyden.

Uremian aktiivihoidossa olevien tyypin 1 diabeetikoiden eloonjäämisennuste on parantunut viime vuosikymmeninä, vaikka heillä on paljon liitännäissairauksia ja lääkityksiä. Tutkimuksemme tulokset viittaavat siihen, että eloonjäämisennusteen parantaminen edelleen saattaa olla mahdollista ehkäisemällä, ajoissa toteamalla ja tehokkaasti hoitamalla näiden potilaiden liitännäissairauksia. Myös aliravitsemuksen, proteinurian, hyperglykemian ja kroonisten tulehdusten hoito sekä tehokas dialyysihoito vaikuttavat tärkeiltä. Lääkityksellä saadaan lääkitystä tarvitsevien potilaiden eloonjäämisennuste samalle tasolle kuin niiden, jotka eivät lääkitystä tarvitse. Satunnaistettuja tutkimuksia tarvitaan löydöstemme varmistamiseksi.

LIST OF ORIGINAL PUBLICATIONS

Haapio Mikko, Helve Jaakko, Groop Per-Henrik, Grönhagen-Riska Carola, Finne Patrik.
Survival of patients with type 1 diabetes receiving renal replacement therapy in 1980–2007.
Diabetes Care 2010; 33:1718–1723

Helve Jaakko, Haapio Mikko, Groop Per-Henrik, Grönhagen-Riska Carola, Finne Patrik.
Comorbidities and survival of patients with type 1 diabetes on renal replacement therapy.
Diabetologia 2011; 54:1663–1669

Helve Jaakko, Haapio Mikko, Groop Per-Henrik, Grönhagen-Riska Carola, Finne Patrik.
Biochemical variables and survival of patients with type 1 diabetes on renal replacement
therapy. Blood Purification. 2014. In press.

Helve Jaakko, Sund Reijo, Haapio Mikko, Groop Per-Henrik, Grönhagen-Riska Carola, Finne
Patrik. Medication among patients with type 1 diabetes and predialytic renal disease. Diabetes
Research and Clinical Practice 2014; 103:510–515

ABBREVIATIONS

ACEI	angiotensin-converting enzyme inhibitor
ARB	angiotensin II receptor blocker
BB	beta-blocker
CAD	coronary artery disease
CCB	calcium channel blocker
CKD	chronic kidney disease
CVD	cerebrovascular disease
ESA	erythropoiesis-stimulating agent
ESRD	end-stage renal disease
HbA1c	Glycosylated hemoglobin, type A1c
HDLC	high-density lipoprotein cholesterol
HF	heart failure
ICD	International Classification of Diseases
IQR	interquartile range
LDLC	low-density lipoprotein cholesterol
LVH	left ventricular hypertrophy
PAD	peripheral artery disease
RR	relative risk of death
RRT	renal replacement therapy
95% CI	95% confidence interval

INTRODUCTION

Diabetic nephropathy is one of the most serious complications of type 1 diabetes, especially when progressed to end-stage renal disease (ESRD). When comparing to the general population, patients with type 1 diabetes complicated by ESRD have a standardized mortality ratio of 18 to 30 (Groop, et al., 2009; Orchard, et al., 2010). Especially in Finland where the incidence of type 1 diabetes is the highest in the world (Harjutsalo, et al., 2008), type 1 diabetes is a major cause of ESRD accounting for 16% of all patients on renal replacement therapy (RRT) (dialysis and kidney transplantation) (Finnish Registry for Kidney Diseases, 2012).

The risk of ESRD has decreased among patients with type 1 diabetes during the past decades (Finne, et al., 2005). However, regardless of continuous development of dialysis treatment and diabetes management, and decreased mortality among other RRT patients (USRDS annual data report, 2013), there is a scarcity of and conflicting data on possible improvements in survival of patients with type 1 diabetes on RRT (Van Dijk, et al., 2005; Villar, et al., 2007). The knowledge of factors that might have an effect on survival among patients with type 1 diabetes on RRT is also limited. Comorbidities have been shown to increase mortality among ESRD patients (van Manen, et al., 2007), and ESRD patients with diabetes (type 1 and type 2 combined) have more comorbidities and worse survival compared to other ESRD patients (Foley, et al., 1997; Lok, et al., 2004). High glycosylated hemoglobin (HbA1c) and cholesterol predict worse survival among patients with type 1 diabetes without ESRD (Rossing, et al., 1996; Shankar, et al., 2007; Soedamah-Muthu, et al., 2008); but when diabetes (type 1 and type 2) is complicated with ESRD the evidence is contradictory (Morioka, et al., 2001; Racki, et al., 2007; Smavatkul, et al., 2007; Williams, et al., 2006; Williams, et al., 2010). Results on the usefulness of hemoglobin, creatinine, and glomerular filtration rate as predictors of mortality among these patients have been conflicting (Conway, et al., 2008; Coronel, et al., 2009; Foley, et al., 1997; Morioka, et al., 2001).

In patients with type 1 diabetes, medication is one of the most important means to improve prognosis and to slow down the progression of renal insufficiency during the predialysis phase. Angiotensin-converting enzyme inhibitors and statins seem beneficial in patients with diabetes in attempt to prevent nephropathy, progression of nephropathy, and premature death (Adult treatment panel III, 2002; Heart Outcomes Prevention Evaluation Study Investigators, 2000; Heart protection Study Collaborative Group, 2002; Lewis, et al., 1993). However, the

results of the association of drug utilization and survival in ESRD patients are contradictory (Foley, et al., 2002; Ishani, et al., 2004; Kestenbaum, et al., 2002) and non-existing among patients with type 1 diabetes and ESRD.

In conclusion, patients with type 1 diabetes on RRT have high risk of premature death, and previous results have shown that factors predicting survival among RRT patients with and without diabetes (type 1 and type 2) are not the same. The knowledge on possible improvement of survival and factors affecting it among patients with type 1 diabetes on RRT is scarce. This knowledge would be essential in attempt to improve survival of these patients. Therefore changes in survival over the last decades were reviewed, along with which factors associate with survival for patients with type 1 diabetes on RRT.

REVIEW OF THE LITERATURE

1. Type 1 diabetes

1.1 Classification

Diabetes mellitus is classified as a group of metabolic disorders where blood glucose concentration is elevated to a level that causes symptoms and possibly organ damage. Elevation of blood glucose is caused by inadequate insulin secretion, decreased insulin action, or both. Symptoms of hyperglycemia include fatigue, polydipsia, polyuria, weight loss, and blurred vision. Life-threatening, acute consequences of hyperglycemia are ketoacidosis and hyperosmolar hyperglycemic nonketotic syndrome. Long-term complications of diabetes are caused by micro- and macrovascular diseases manifesting especially in kidneys, eyes, extremities, peripheral and autonomic nerves, and the cardiovascular system.

The definition of diabetes is based on plasma glucose measurements. Diabetes is diagnosed if fasting plasma glucose is ≥ 7.0 mmol/l or plasma glucose is ≥ 11.1 mmol/l two hours after 75 g oral glucose intake or HbA1c is $\geq 6.5\%$ (48 mmol/mol). If one plasma glucose measurement is over 11.1 mmol/l combined with symptoms implying diabetes (thirst, polyuria, weight loss), a diabetes diagnosis is warranted (American Diabetes Association, 2013; World Health Organization, 2006). These limits are set to the level above which premature mortality, microvascular, and cardiovascular complications resulting from hyperglycemia are increased. According to World Health Organization guidelines (2006), intermediate hyperglycemia is diagnosed if fasting plasma glucose is 6.1–6.9 mmol/l (impaired fasting glucose) or plasma glucose is 7.8–11.0 mmol/l two hours after oral ingestion of 75 g glucose load (impaired glucose tolerance). An oral glucose test should be performed, if fasting glucose concentration is 6.1–6.9 mmol/l. Otherwise, 30% of the patients with inadequate insulin response to glucose intake will not be diagnosed as having diabetes. The American Diabetes Association (2013) has set lower limits to detect people with increased risk for diabetes. According to these guidelines, intermediate hyperglycemia is diagnosed when fasting plasma glucose concentration is 5.6–6.9 mmol/l or HbA1c 5.7–6.4%.

Diabetes has traditionally been divided into two groups. In type 1 diabetes, lack of insulin secretion is caused by immune-mediated destruction of pancreatic insulin-secreting islet beta-

cells. Type 2 diabetes is caused by deficient insulin action, when response to insulin in target tissues is diminished (insulin resistance) and insulin secretion is inadequate to compensate this (National Diabetes Data Group, 1979). However, there is a wide overlap between these two groups as a metabolic syndrome with insulin resistance can be found in over one-third of the patients with type 1 diabetes. Among patients with type 1 diabetes and end-stage renal disease, metabolic syndrome is even more common (Thorn, et al., 2005). A few decades ago, all children with diabetes were diagnosed as having type 1 diabetes, but differentiation of diabetes diagnosis by age is misleading. Obesity among children is increasing (Li, et al., 2008), and hence a notable proportion of children with diabetes have type 2 diabetes, especially in populations with a low incidence of type 1 diabetes (CDC, 2011; Dabelea, et al., 2007). Diagnostic problems also occur in young patients with diabetes who have pancreatic autoantibodies but otherwise phenotype of type 2 diabetes (Klingensmith, et al., 2010; Reinehr, et al. 2006). In addition to type 1 and type 2 diabetes, there are other forms of diabetes. Latent autoimmune diabetes in adults (LADA) is pathophysiologically similar to type 1 diabetes, but disease progress is slower and it is diagnosed usually in adulthood. Clinical outcome of the disease is similar to type 2 diabetes, and insulin therapy is not required at the time of diagnosis, but insulin dependency usually develops over time (Pozzilli, et al., 2001). Maturity-onset diabetes of the young (MODY) is heterogenous group of inheritant disorders causing nonketotic diabetes. MODY develops usually before 25 years of age, and is typically caused by pancreatic beta-cell dysfunction. The disease can result from mutation in one of at least six genes expressing in beta-cells (Fajans, et al., 2001). Other forms of diabetes include gestational diabetes and diabetes caused by loss of pancreatic tissue because of inflammation, trauma, or surgery. Consequently, diagnosis of type 1 diabetes is not always clear and development of genetic and molecular characterisation of diabetes may lead to more defined subgroups and treatment strategies (Tuomi, et al., 2013).

1.2 Pathogenesis

Type 1 diabetes is an autoimmune disease, where autoreactive T-cells and autoantibodies cause cellular-mediated destruction of the islet beta-cells of the pancreas (Bluestone, et al., 2010). Autoantibodies to islet cells, insulin, glutamic acid decarboxylase, and tyrosine phosphatases IA-2 and IA-2 beta are present in 85–90% of patients when the disease is diagnosed (American Diabetes Association, 2013; Expert Committee on the Diagnosis and

Classification of Diabetes Mellitus, 1997). There is also strong association to some HLA alleles (Huang, et al., 1996), and patients are prone to other autoimmune diseases (Larizza, et al., 2012).

The rate of beta-cell destruction determines the time of the onset of the disease. When destruction is fast, dependence on insulin therapy appears rapidly, and patients are at risk of severe hyperglycemia and ketoacidosis. When the disease progresses slowly, residual insulin secretion can prevent ketoacidosis for many years. The incidence of type 1 diabetes has increased rapidly during the last decades (Green, et al., 2001). Because of improved survival, nowadays only few patients with type 1 diabetes die before reaching the age of fertility. This enables the possibility to transfer the genetic risk of type 1 diabetes to offspring. The risk of type 1 diabetes is increased in the offspring of patients with type 1 diabetes of Caucasoid origin, and is 2–4% if the mother is affected, and 5–8% if the father is affected compared to 0.4% with no family history (Groop, et al., 2014). Nevertheless, genetic factors cannot alone explain this increase, and environmental factors seem to play an important role at onset (Hermann, et al., 2003). A study from Finland showed that the prevalence of type 1 diabetes among Somali children born in Finland was similar to the background population, although the prevalence of type 1 diabetes in Somalia is markedly lower than in Finland. This highlights the importance of exogenous factors in the development of type 1 diabetes (Oilinki, et al., 2011). However, knowledge remains scarce regarding the environmental factors that are sensitizing to the onset of type 1 diabetes. Enterovirus infection and dietary antigens (e.g. bovine insulin) are the strongest candidates for the factors that might trigger the process leading to type 1 diabetes (Coppieters, et al., 2011; Knip, et al., 2011). Gut microbiota may expose the immune system to these triggering factors (Vaarala, 2012). Another explanation for the growing incidence in children is lack of environmental factors that were previously present, which would cause the underused immune system to attack its own cells (Gale, 2005).

1.3 Epidemiology

The incidence of type 1 diabetes varies widely in the world as was shown in a large multinational study (The Diamond Project Group, 2006). In this study, the age-adjusted incidence was the lowest in China and Venezuela (0.1 per 100 000 per year) and the highest in Finland (40.9 per 100 000 per year) (Figure 1).

Figure 1. Incidence of type 1 diabetes worldwide 1990-1999

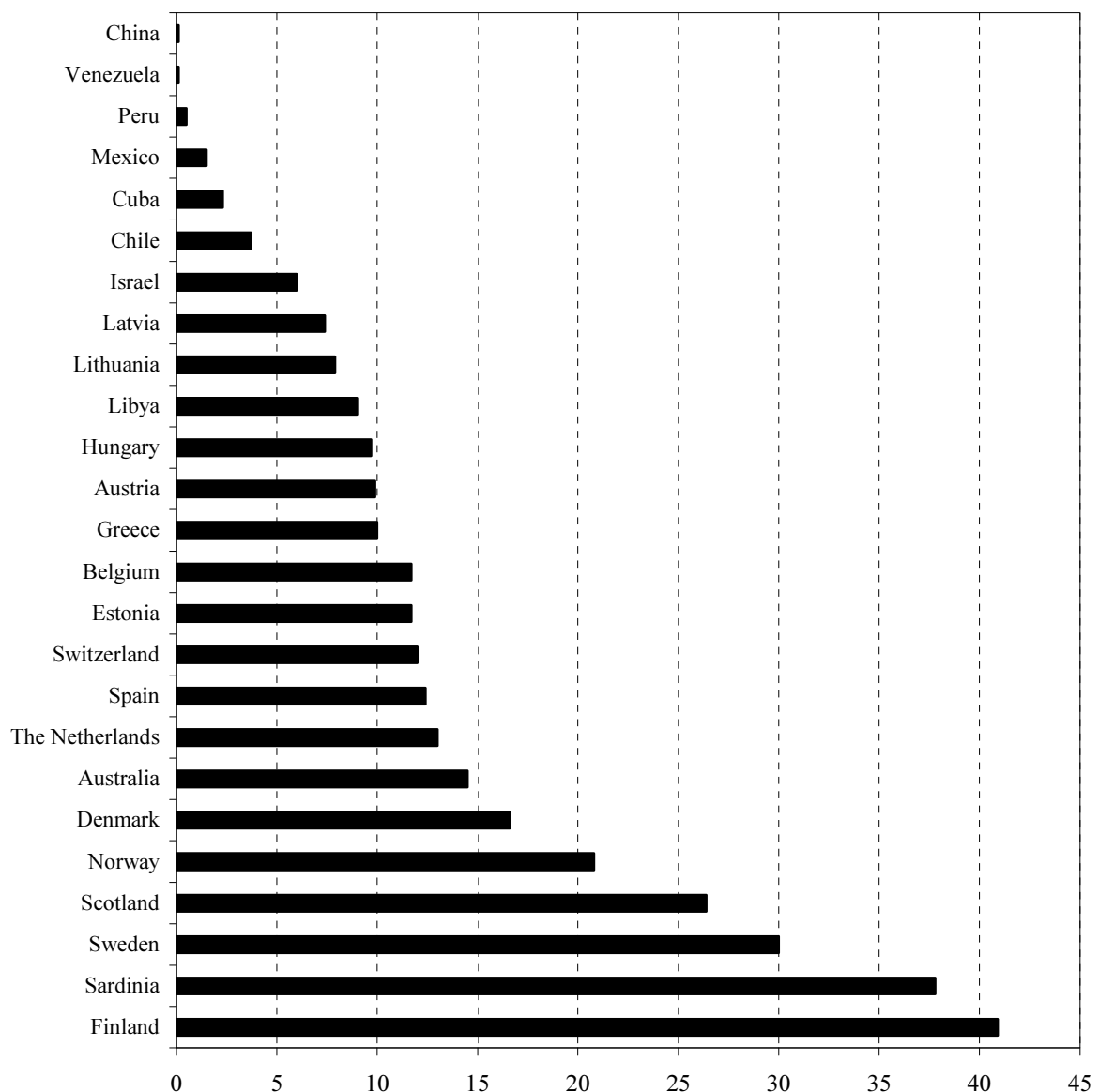


Figure modified from The Diamond Project Group, 2006

The incidence of type 1 diabetes in Finnish children has increased from 31.4 per 100 000 per year in 1980 to 64.2 per 100 000 per year in 2005 (Harjutsalo, et al., 2008). The increase has been most remarkable in children aged 0–4 years. However, this increase has been followed by a plateau since 2005 (Harjutsalo, et al. 2013), which is in line with the results from Sweden (Berhan, et al., 2011). Similar results of increasing incidence are reported from other European countries with 3.2% annual increase in incidence (Green, et al., 2001). Seasonal alteration in incidence was also shown; onset of the disease was less common during the

summer months. This implies to a role for environmental factors in the onset of type 1 diabetes. Although the incidence in children has increased, the overall incidence has not increased in Belgium and Sweden, because the incidence among adults has decreased (Pundziute-Lyckå, et al., 2002; Weets, et al., 2002). This could mean that type 1 diabetes manifests earlier in age than previously. However, a recent study in Finland reported that the incidence among young adults (15–39 years old) increased annually by 3.9% during the follow-up in 1992–2001. The increase in incidence was similar to that in children (4.2%) (Lammi, et al., 2008). Boy-to-girl ratio in type 1 diabetes incidence is 0.9–1.0 in children, but male excess is noted for adult-onset disease by ratio 1.6 (Harjutsalo, et al., 2008, Weets, et al., 2002). The onset of type 1 diabetes has shifted to earlier age, and the overall incidence has increased at least in Finland. However, the reason for this change remains unclear.

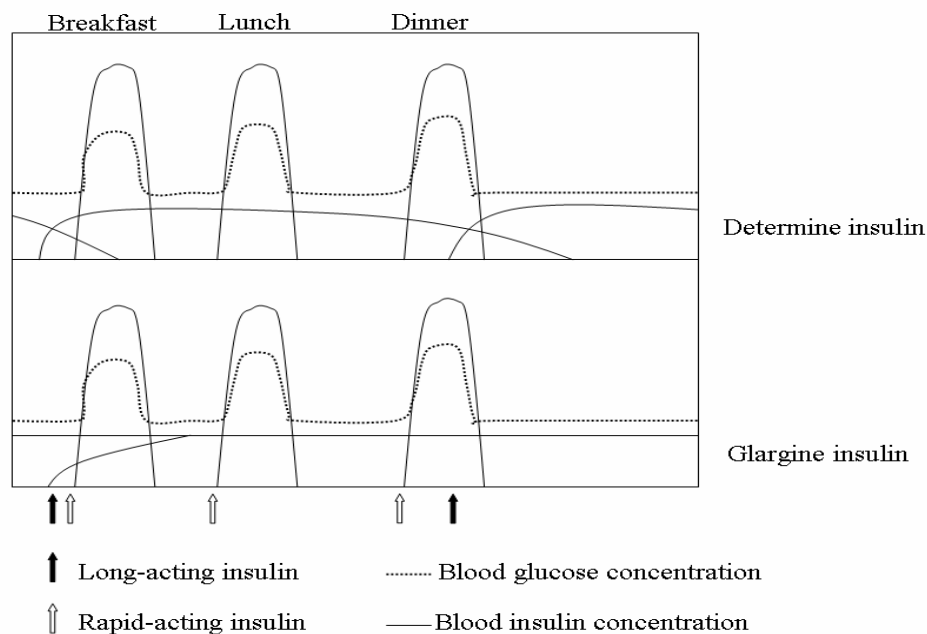
1.4 Treatment

Diabetes was recognized as a clinical entity in 1812, and there was no effective treatment until the discovery of insulin in 1923. Insulin deficiency led to patient death within weeks to months after diagnosis without treatment (Polonsky, 2012). The treatment of type 1 diabetes is based on insulin therapy. Disposable insulin syringes reached wider use in the 1970s, and home glucose monitoring and semisynthetic and synthetic human insulin become available in the 1980s. The emergence of rapid-acting insulin regimens in the 1980s led to the development of a multiple insulin injection treatment, where long-acting insulin is injected subcutaneously 1–2 times per day and rapid-acting insulin administered before a meal, which enables more stable blood glucose control (Figure 2). Another option is insulin-pump therapy, which provides continuous subcutaneous insulin infusion and a possibility to achieve better glycemic control (Pickup, et al., 2012). Regular glucose self-monitoring several times a day is required to adjust doses of insulin therapy. Development of continuous glucose monitoring combined with insulin-pump therapy will probably make blood glucose control better controllable in the future (Siegmund, et al., 2013).

Normoglycemia without the fear of hypoglycemia can be obtained by pancreas transplantation (Fioretto, et al., 1993). However, surgical complications and immunosuppressive treatment are the main problems of this treatment (Gruessner, et al., 2011). Transplantation of human pancreatic islet cells can also provide an option to treat type 1 diabetes (Robertson, 2010; Vaithilingam, et al., 2011). The first results from pancreatic islet transplantations were

promising (Shapiro, et al., 2000), but a five-year follow-up study after islet transplantation showed that only ~10% maintained insulin independence (Ryan, et al., 2005). In the future, newly diagnosed type 1 diabetes could be treated with antigen-specific treatments. These immune therapies (vaccination, and immunosuppressive and immunomodulative agents) act by modulating T-cell action in attempt to stop the autoimmune destruction of pancreatic beta-cells (Bluestone, et al., 2010; Michels, et al., 2011; Peakman, 2012).

Figure 2. Multiple insulin injection treatment of type 1 diabetes



1.5 Diabetic nephropathy

Years of hyperglycemia can cause micro- and macrovascular complications. Macrovascular complications may affect heart, brain, and peripheral blood vessels, and microvascular complications are manifested primarily in eyes, peripheral and autonomic nerves, and kidneys. Early diagnosis and effective treatment of diabetic nephropathy is essential, because it increases mortality significantly (Groop, et al., 2009; Orchard, et al., 2010).

1.5.1 Classification

Proteinuria and progression from hyperfiltration to gradual decrease of glomerular filtration rate are the signs of nephropathy in type 1 diabetes. Diabetic nephropathy, especially when proceeded to clinical albuminuria, increases the risk of cardiovascular diseases (Tuomilehto, et al., 1998) and decreases survival significantly (Borch-Johnsen, et al., 1985, Groop, et al., 2009, Rossing, et al., 1996).

Microalbuminuria as the sign of diabetic nephropathy is diagnosed when the urinary albumin excretion rate is repeatedly 20–200 $\mu\text{g}/\text{min}$. Macroalbuminuria means albumin excretion rate $\geq 200 \mu\text{g}/\text{min}$. An alternative way to examine urinary albumin excretion is the measurement of albumin and creatinine from a urine sample. Albumin/creatinine values 2.5–25 mg/mmol in men and 3.5–35 mg/mmol in women are considered to be microalbuminuria and values above those macroalbuminuria. Kidney function is normally assessed by glomerular filtration rate (GFR). When kidney function deteriorates and GFR decreases to lower than 15 ml/min , a patient is classified as having end-stage renal disease (ESRD) and requires renal replacement therapy (RRT). New classification of chronic kidney disease (CKD) divides it into stages 1 to 5, and stage 5 CKD equals the term ESRD used in this text.

Measurement of inulin clearance is the gold standard for the determination of GFR (Smith, 1951), but not suitable for screening. Serum creatinine is commonly used to evaluate kidney function and calculate GFR. The formulas proposed by Cockcroft and Gault (Cockcroft, et al., 1976), Modification of Diet in Renal Disease (MDRD) (Levey, et al., 1999), and the chronic kidney disease epidemiology collaboration (CKD-EPI) equation (Levey, et al., 2009) are the most commonly used to estimate GFR. MDRD is suitable for GFR estimation in advanced CKD, and the CKD-EPI equation performs better at higher GFRs (Earley, et al., 2012). Because these formulas cannot eliminate all other factors than creatinine filtration affecting serum creatinine concentration, other serum markers for renal function have been studied. Serum cystatin C appears to be better than creatinine to estimate GFR (Kyhse-Andersen, et al., 1994; Simonsen, et al., 1985). Higher costs of cystatin C and established clinical practise in creatinine use have, however, prevented widespread use of cystatin C.

1.5.2 Epidemiology

Table 1 shows reported cumulative incidence rates of nephropathy (persistent proteinuria) in patients with type 1 diabetes.

Table 1. Incidence of nephropathy among patients with type 1 diabetes

Study, year	Country	Year of type 1 diabetes diagnosis	Number of patients	Follow-up	Incidence of diabetic nephropathy	Comments
Andersen, et al., 1983	Denmark	Before 1953	1303	40 years	45%	A male preponderance
Kofoed-Enevoldsen, et al., 1987	Denmark	1933–1972	2890	At least 11 years	20%	Incidence peak after 15–17 years from diabetes diagnosis
Bojestig, et al., 1994	Sweden	1961–1980	213	20 years	10%	Decline in incidence from 28% to 6% during study period
Rossing, et al., 1995	Denmark	1965–1979	356	15 years	16–20%	No decline in incidence
Hovind, et al., 2003	Denmark	1965–1984	600	20 years	14–31%	Significant decline in incidence during study period

Nephropathy was diagnosed if at least two urine samples contained albumin ≥ 300 mg/24 h or ≥ 300 mg/liter.

An older study reported 45% cumulative incidence of nephropathy after 40 years from the diagnosis of type 1 diabetes (Andersen, et al., 1983). The incidence of nephropathy decreased 30% from patients with type 1 diabetes diagnosed in the 1930s to patients diagnosed in the 1950s (Kofoed-Enevoldsen, et al., 1987). A Swedish study showed 20-year cumulative incidence decreasing from 28% in patients diagnosed with type 1 diabetes in 1961–1965 to 5.8% in patients diagnosed in 1971–1975 (Bojestig, et al., 1994), and Hovind, et al. (2003) reported similar results: The 20-year incidence of type 1 diabetic nephropathy decreased from 31% to 14% when the patients with type 1 diabetes diagnosed in 1965–1969 were compared to the patients diagnosed in 1979–1984. However, a Danish study of patients with type 1 diabetes diagnosed in 1965–1979 could not find any decline in the incidence of diabetic nephropathy (Rossing, et al., 1995). The reason for these conflicting results is unknown. Some of the patients with nephropathy develop end-stage renal disease. Finne et al (2005) reported that the cumulative incidence of end-stage renal disease among patients with type 1

diabetes has declined, and is 2.2% at 20 years and 7.8% at 30 years after diabetes diagnosis. The peak of the incidence of diabetic nephropathy is seen after 15–17 years of diabetes duration (Andersen, et al., 1983; Kofoed-Enevoldsen, et al., 1987).

1.5.3 Development

Nephropathy in type 1 diabetes usually develops slowly as shown in Table 2.

Table 2. Development of nephropathy in type 1 diabetes

Stage	Time from diagnosis of diabetes	Glomerular filtration rate	Albumin excretion	Blood pressure
Acute renal hypertrophy/hyperfunction	Present at diagnosis, reversible	Increased by 20–50%	Normal or increased but reversible	Normal
Normoalbuminuria	0–5 years	Increased by 20–50%	Normal	Normal
Microalbuminuria	6–15 years ^a	Normal–supranormal, declining	Increase \approx 20% / year ^b	Incipient increase \approx 3 mmHg/year ^b
Overt diabetic nephropathy	15–25 years ^a	Decline \approx 10 ml/min/year ^b	Progressive clinical proteinuria ^b	High blood pressure, increase by \approx 5 mmHg /year ^b
End-stage renal disease	\geq 25 years ^a	$<$ 10 ml/min	Often some decline due to nephron closure	High ^b

^aIn patients who develop diabetic nephropathy

^bWithout treatment

Table modified from Mogensen, 1999

Microalbuminuria is typically the first sign of nephropathy (Mogensen, 1987). Pathological changes in kidneys start from increased glomerular size and increased basement membrane thickness, and develop gradually to mesangial expansion and advanced glomerulopathy. A typical finding in kidney biopsy is nodular glomerulosclerosis, but diffuse glomerulosclerosis is also possible (Østerby, 1996). Progressive proteinuria is of glomerular origin and is followed by decrease in glomerular filtration rate. Hyperglycemia and hypertension are the main factors in the development of nephropathy, but genetic factors play an important role (Mogensen, 1999; Parving, 1998). Microalbuminuria and macroalbuminuria can be reversible

with intensive treatment of hyperglycemia and hypertension (The diabetes control and complications trial research group, 1993; Lewis, et al., 1993 and 2001).

1.5.4 Risk factors

Microalbuminuria is a risk factor for progression of diabetic nephropathy and risk of death increases with severity of renal disease (Groop, et al., 2009; Viberti, et al., 1982; Yokoyama, et al., 2011). Only some microalbuminuria patients develop macroalbuminuria or ESRD (Forsblom, et al., 1992). However, already borderline microalbuminuria 14–21 µg/min is associated with significantly increased risk of renal disease progression and cardiovascular death (Rachmani, et al., 2000)

Hyperglycemia is a major factor in the development of diabetic nephropathy (Alaveras, et al., 1997, Waden, et al., 2009). The risk of microalbuminuria increases rapidly when HbA1c is over 8.1% (Krolewski, et al., 1995), and the incidence of diabetic nephropathy decreases and the risk of declined GFR is significantly lower with intensive treatment of hyperglycemia (The diabetes control and complications trial research group, 1993; The DCCT/EDIC Research Group, 2011).

Hypertension is essentially associated with diabetic nephropathy. Blood pressure increases during the progression of renal disease, but hypertension is also a risk factor of nephropathy (Mogensen, 1999; Rossing, et al., 1993) and antihypertensive treatment reduces progression of diabetic nephropathy (Casas, et al., 2005). Guidelines recommend angiotensin-converting-enzyme inhibitors (ACEI) or angiotensin II receptor blockers (ARB) when treating hypertension in patients with diabetic nephropathy. A randomized trial showed that ACEI use reduces the progression of nephropathy in patients with type 1 diabetes (Lewis, et al., 1993), and two randomized studies reported on the beneficial effect of ARBs on nephropathy among patients with type 2 diabetes (Brenner, et al., 2001; Lewis, et al., 2001). However, a meta-analysis could not show an additional renoprotective effect of ACEIs or ARBs beyond lowering blood pressure in diabetic patients (Casas, et al., 2005). Although dietary sodium intake restriction is recommended for treatment of hypertension, type 1 diabetic patients with the lowest sodium intake seem to have higher risk of ESRD and mortality (Thomas, et.al, 2011).

Mannose-binding lectin and high-sensitivity C-reactive protein as the markers of low-grade inflammation has been shown to associate with increased risk of progression of diabetic nephropathy (Hansen, et al., 2010).

Dyslipidemia has been shown to associate with microproteinuria and declined GFR in type 1 diabetes patients (Demirel, et al., 2013; Bulum, et al., 2013), and these results suggest that dyslipidemia may play a role in the pathogenesis of diabetic nephropathy. Also metabolic syndrome and physical inactivity increases the risk for diabetic nephropathy (Thorn, et al., 2009; Wadén, et al., 2008).

Cigarette smoking increases the incidence and the risk of progression of diabetic nephropathy. Albuminuria can also improve if smoking is ceased (Chase, et al., 1991; Christiansen, 1978; Sawicki, et al., 1994).

Genetic susceptibility also plays a role in the development of diabetic nephropathy, and the strongest associations with diabetic nephropathy have been shown at the FRMD3 and CARS genomic loci (Pezzolesi, et al., 2009). Puberty and sex hormones may have an influence on development and progression of diabetic nephropathy, because there is markedly higher risk of ESRD due to diabetic nephropathy among male compared to female patients, especially when diabetes is diagnosed after puberty (Möllsten, et al., 2010).

Table 3. Risk factors of development and progression of nephropathy in patients with type 1 diabetes

Study, year	Country	Patients	Number of patients	Prognostic factor	Results
Krolewski, et al., 1995	United States	IDDM	1613	HbA1c	Risk of microalbuminuria increases rapidly when HbA1c is over 10.1%
Waden, et al., 2009	Finland	Type 1 diabetes	2102	HbA1c	HbA1c is independently associated with progression of diabetic nephropathy
The DCCT/EDIC Research Group, 2011	United States	Type 1 diabetes	1441	Hyperglycemia	The risk of an impaired GFR was lower among persons treated with intensive diabetes therapy
Rossing, et al., 1993	Denmark	IDDM and proteinuria	41	Diastolic blood pressure	Diastolic blood pressure is correlated with decline in glomerular filtration rate
Viberti, et al., 1982	NA	IDDM	87	Microalbuminuria	Microalbuminuria predicts progression of diabetic nephropathy
Bulum, et al., 2013	Croatia	Type 1 diabetes	313	Dyslipidemia	Dyslipidemia is associated with an impaired GFR
Thorn, et al., 2009	Finland	Type 1 diabetes	3783	Metabolic syndrome	Metabolic syndrome is a risk factor for progression of diabetic nephropathy
Chase, et al., 1991	United States	IDDM	359	Cigarette smoking	Smoking is associated with development and progression of nephropathy
Hansen, et al., 2010	Finland	Type 1 diabetes	1564	Inflammation	Low-grade inflammation associates with progression of diabetic nephropathy
Pezzolesi, et al., 2009	United States	Type 1 diabetes	1705	Genes	FRMD3 and CARS genomic loci are associated with susceptibility to diabetic nephropathy
Möllsten, et al., 2010	Sweden	Type 1 diabetes	11 681	Gender and age at diabetes diagnosis	The risk of ESRD due to diabetic nephropathy is the highest among male diagnosed at age 20–34 years

IDDM; Insulin dependent diabetes mellitus, NA; Not available

2. End-stage renal disease

2.1 Etiology and epidemiology

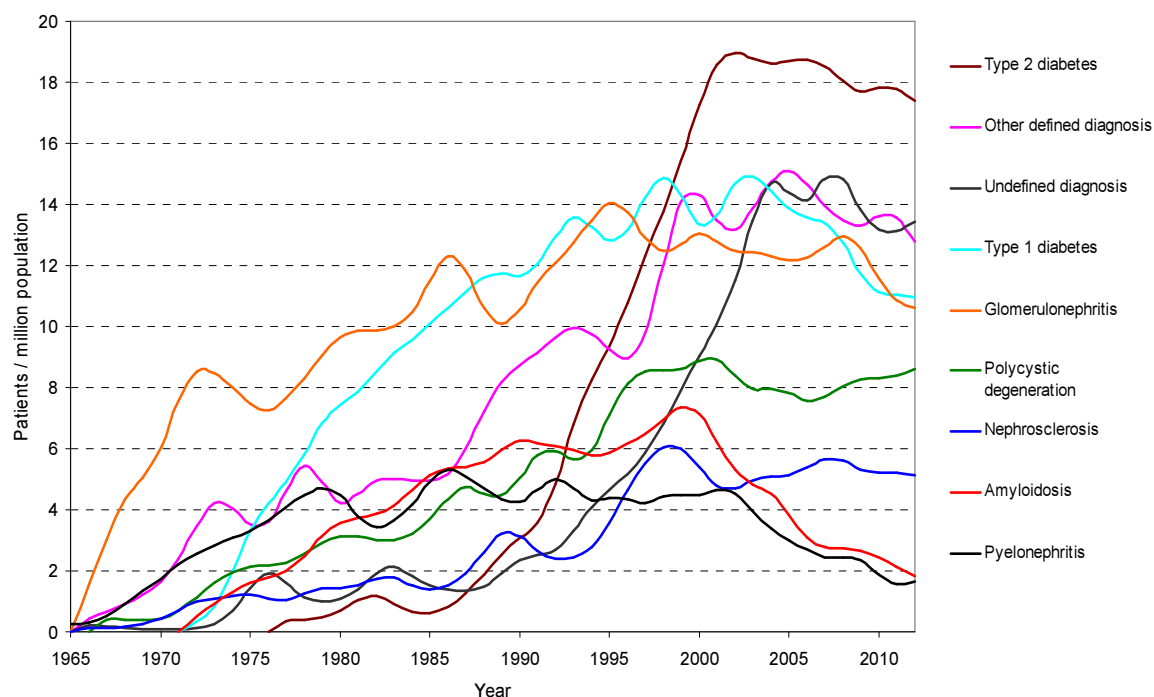
In end-stage renal disease (ESRD) the kidneys are unable to maintain low levels of urea, normal hematocrit, sodium and potassium, and water and acid-base balance. Therefore renal replacement therapy (RRT) is needed (Mitch, 2012). Loss of renal function without RRT would cause life-threatening hyperkalemia, acidosis, uremia, and/or fluid retention. Even on RRT, patients with ESRD manifest several clinical problems: e.g. equilibrium of calcium and phosphorus leading to calcification of vessels and soft tissues, and renal osteodystrophy, hypertension, anemia, and changes in blood coagulation.

The incidence of ESRD varies widely globally and is usually assessed by the incidence of RRT patients. However, ESRD patients' inclusion criteria to RRT varies between countries. According to the ERA-EDTA registry (Annual report 2011), the annual incidence of RRT in Europe varies from 85 new patients per million population in Finland to 203 per million in Greece. In Mexico, the annual incidence is 527 new patients per million population and in Bangladesh only 32 patients per million population (USRDS annual data report: 2013 Atlas of CKD and ESRD). The difference in the incidence is partly explained by the available funding, especially in developing countries. However, an increased number of patients with diabetes and ESRD explain the high incidence rates in some countries. For example, in Mexico, diabetes is the cause of end stage renal disease in almost 60% of the patients starting RRT. Type 1 and type 2 diabetes are the most important causes to start RRT in Finland (Figure 3). In most of the countries, type 2 diabetes is a far more common cause of ESRD than type 1 diabetes, but in the countries with a high incidence of type 1 diabetes like Finland, Sweden, Denmark, and the United Kingdom, type 1 diabetes is the cause of ESRD in 40% of the diabetes-caused ESRD cases. In Finland, the incidence of RRT caused by type 2 diabetes increased remarkably in the 1990s, but has been stable since 2000 as well as the incidence of new RRT patients with glomerulonephritis, polycystic kidney disease, and nephrosclerosis. The incidence of ESRD caused by type 1 diabetes has decreased slightly after the year 2000, and the incidence of ESRD caused by amyloidosis and pyelonephritis has decreased drastically (Figure 1).

Approximately two-thirds of the ESRD patients are men, and the median age is around 60–70 years at the start of RRT. Kastarinen et al (2010) reported that obesity, hypertension, diabetes, and male gender are independent risk factors for ESRD. The incidence of RRT has been

rather stable during the last decade. However, the prevalence of RRT has increased at the same time due to improved survival. The prevalence of RRT in Finland is 805 patients per million population, and varies elsewhere from 159 RRT patients per million population in the Philippines to 2309 per million population in Japan (Finnish Registry for Kidney Diseases, Report, 2012; USRDS annual data report: 2013 Atlas of CKD and ESRD).

Figure 3. Incidence of RRT according to ethiology



Finnish Registry for Kidney Diseases, Report, 2012

2.2 Treatment

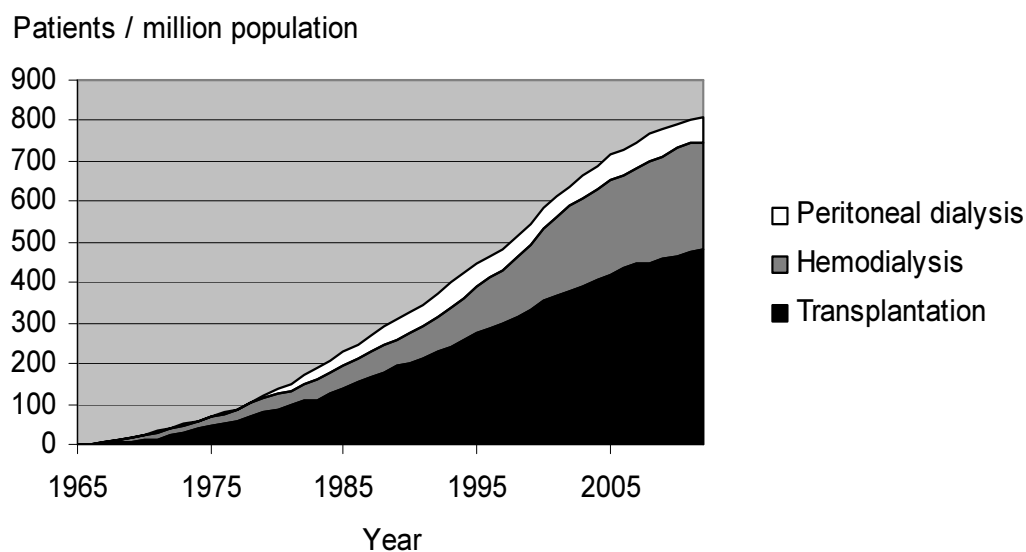
2.2.1 Hemodialysis and peritoneal dialysis

Hemodialysis is the most common treatment modality at the initiation of RRT. It has been used in chronic kidney disease since the 1960s. Infections are common complications with hemodialysis catheters and therefore arteriovenous fistula or graft is a more preferable vascular access in chronic hemodialysis (Bagdasarian, et al., 2012). Diabetes, age, and peripheral artery disease may provide problems in arteriovenous fistula patency (Smith, et al.,

2012). Hemodialysis three times per week at hospital is the most common protocol, but daily dialysis at home provides more flexibility for the patient.

Peritoneal dialysis allows more independence than hemodialysis, costs are significantly lower, and survival rates are comparable to hemodialysis (Fenton, et al., 1997; Mehrotra, et al., 2011; Rodriquez, et al., 2011; Sinnakirouchenan, et al., 2011). Peritoneal dialysis can be a beneficial choice for younger patients without diabetes during the first years on RRT, but older patients with diabetes seem to benefit from hemodialysis, and hemodialysis has a survival advantage after longer duration of RRT (Collins, et al., 1999; Heaf, et al., 2002; McDonald, et al., 2009; Vonesh, et al., 2006). Infection is the most common problem in peritoneal dialysis and may prevent the use of it. Increased peritoneal permeability, loss of ultrafiltration, and peritoneal fibrosis, processes accelerated in diabetes, can also lead to technique failure (Locatelli, et al., 2004).

Figure 4. Prevalence of RRT at end of year in Finland according to type of treatment



Finnish Registry for Kidney Diseases, Report, 2012

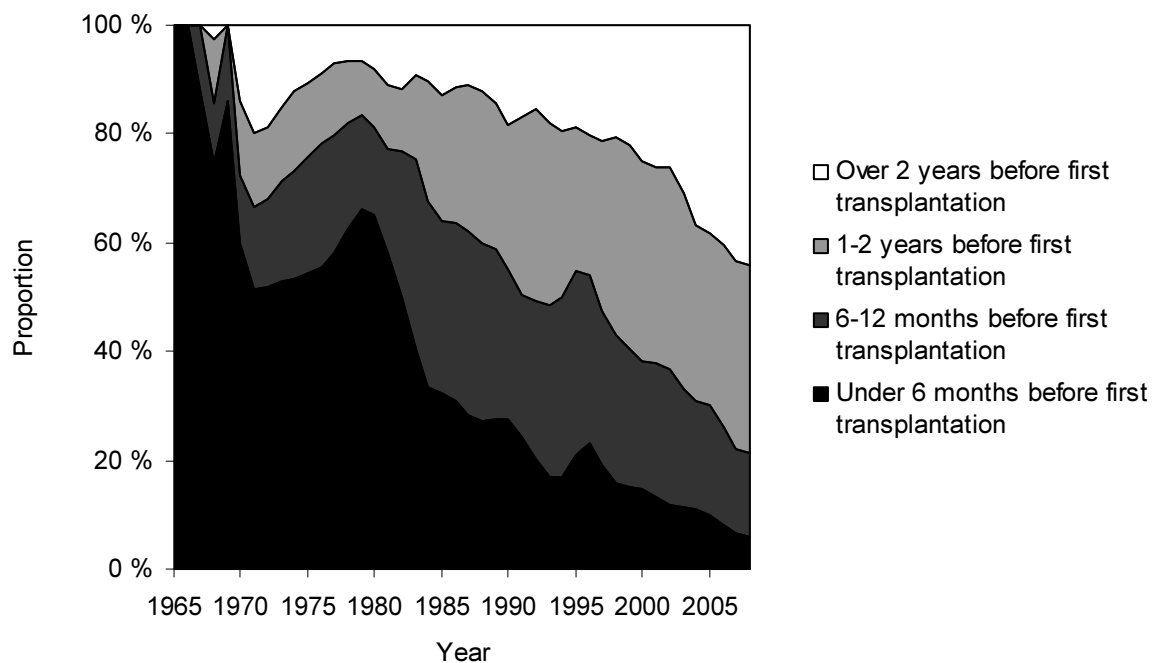
In Finland in 2012, 7% of the RRT patients used peritoneal dialysis, 33% hemodialysis, and almost 60% had a functioning kidney transplant (Figure 4) (Finnish Registry for Kidney Diseases, Report 2012). Among patients with type 1 diabetes as the cause of ESRD, the corresponding figures were 10% in peritoneal dialysis, 23% in hemodialysis, and 67% with kidney transplant. In 2011, peritoneal dialysis was used in 19% of dialysis patients in Finland,

which is equal to other nordic countries. However, peritoneal dialysis was a much less common dialysis modality for example in the United States (7%) and Japan (3%), and far more common in Hong Kong (74%) and Mexico (49%) (USRDS annual data report, 2013).

2.2.2 Kidney transplantation

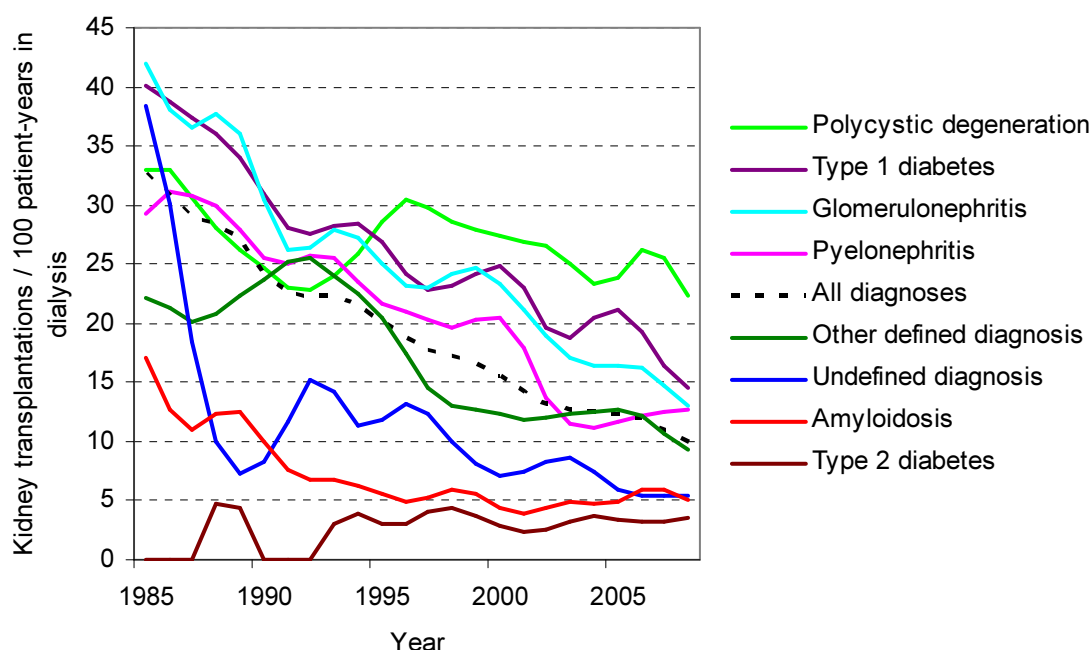
Successful kidney transplantation offers the best quality of life for ESRD patients (Jofré, et al., 1998). Survival in patients treated with kidney transplantation is better than with hemodialysis or peritoneal dialysis (USRDS annual data report, 2013; ERA-EDTA annual report, 2011). However, patient groups of transplant recipients and non-recipients are not comparable and this causes a bias, which is almost impossible to control by statistical adjustments. Unfortunately the number of patients on a kidney transplantation waiting list far exceeds the number of donors. The annual number of transplantations in Finland has remained about the same for 20 years and the prevalence of RRT patients has increased, which has led to increased waiting time on dialysis before first kidney transplantation (Figure 5).

Figure 5. Time elapsed before first kidney transplantation after start of RRT (Finnish Registry for Kidney Diseases 1965–2008)



Type 1 diabetes is the most common cause of kidney transplantation in Finland, but when related to patient-years in dialysis, patients with polycystic kidney disease receive kidney transplant most often. Overall, the number of kidney transplantations related to patient-years in dialysis has decreased markedly (Figure 6). Almost all kidney transplants (98%) come from deceased donors in Finland, but for example in the United Kingdom, Norway, Sweden, and Denmark, more than one-third of kidney transplant recipients receive an organ from a living donor. This reflects the lower transplantation rates in Finland in 2010 (33 per million population) compared to the prementioned countries (41–61 per million population) (ERA-EDTA annual report, 2011). However, the prevalent rate of functioning grafts in Finland 2011 (474 per million population) was comparatively good on an international level (USRDS annual data report, 2013).

Figure 6. Kidney transplantations related to patient-years in dialysis according to diagnosis (Finnish Registry for Kidney Diseases 1985–2008)



Patients with type 1 diabetes and ESRD can also be treated by simultaneous kidney-pancreas transplantation, which enables discontinuity or reduction of insulin treatment and achievement of better glucose balance.

However, transplantation has risks associated with surgical procedures, and immunosuppressive therapy after transplantation can cause side effects, predispose to infections, and have interactions with other medication. Before the millenium shift, the combination of cyclosporin, azathioprine, and steroids was the most common immunosuppressive medication at the end of the year that kidney transplantation was performed. Thereafter, the most common combination has been cyclosporin and mycophenolate in various combinations. Tacrolimus is used as an alternative to cyclosporin in a quarter of the transplant recipients. The use of steroids has diminished considerably during the past decade (Finnish Registry for Kidney Diseases, Report 2008).

2.3 Survival

2.3.1 Survival and causes of death

Mortality among patients on RRT is high, and five-year survival is 47%. Due to better survival of patients with kidney transplantation, patients on dialysis have even worse survival; only 36–39% of them are alive after five years on dialysis, and adjusted mortality ratio is 6.5–7.9 times greater than for individuals in the general population (ERA-EDTA annual report, 2011; USRDS annual data report, 2013). Age- and gender adjusted mortality in dialysis patients is almost two-fold higher than in patients with cancer or chronic heart failure illustrating the severity of ESRD (USRDS annual data report, 2013). Survival of kidney transplant recipients is better with five-year survival of 85–94%, but adjusted mortality ratio is still 1.0–1.5 times as high as in the general population (ERA-EDTA annual report, 2011; USRDS annual data report, 2013).

Cardiovascular causes of death are the most common among ESRD patients, being the cause of death in approximately half of the cases. Infections are the cause of death in a quarter of the patients, and cancer, or disease that caused kidney failure both in less than 10% of the ESRD patients (Finnish Registry for Kidney Diseases, Report 2008). Although cardiovascular mortality is 10–20 times higher in dialysis patients than in the general population, noncardiovascular mortality is equally increased. Consequently, increased mortality is not caused by excess cardiovascular mortality alone (de Jager, et al., 2009).

2.3.2 Risk factors

Most of the risk factors affecting survival of patients on RRT are similar to those of individuals in the general population. However, there are differences and the magnitude of the influence of risk factors may differ.

Age at the start of RRT is one of the most important mortality risk factors (Postorino, et al., 2009; Van Mannen, et al., 2007), but gender seems to have no effect on survival in ESRD patients in contrast to the general population (Villar, et al., 2007; Wallen, et al., 2001). Comorbidities and their severity increase mortality among these patients (Khan, et al., 1993; Lucas, et al., 2003; Miskulin, et al., 2003). Patients with ESRD and diabetes have worse survival than other patients on RRT (Foley, et al., 1997; Lok, et al., 2004; Postorino, et al., 2009; van Mannen, et al., 2007; Wallen, et al., 2001). No survival difference between patients with diabetes as the cause of renal disease and as a comorbid condition have been found (Schroijen, et al., 2011). Cardiovascular disease is the most common cause of death in ESRD patients, and understandably the presence of cardiovascular disease is associated with higher mortality (Mailloux, et al., 1996; van Mannen, et al., 2007). Heart failure (Foley, et al., 1997), left ventricular hypertrophy (Stack, et al., 2002), cancer, cerebrovascular disease, peripheral artery disease (Ono, et al., 2003; van Mannen, et al., 2007), hypertension (Lucas, et al., 2003; Mailloux, et al., 1996), and low BMI (Postorino, et al., 2009) have also been shown to associate with increased mortality among ESRD patients.

Biochemical variables can also be used to estimate mortality risk among these patients. Hypoalbuminemia reflects poor nutritional status, liver malfunction, excessive proteinuria, inflammation, fluid retention, and overall morbidity. Consequently, hypoalbuminemia is a strong predictor of death among ESRD patients (Culp, et al., 1996; Lackson, et al., 2009; Mailloux, et al., 1996). ESRD usually causes anemia and is treated with erythropoiesis-stimulating agents. Better survival has been shown to associate with higher hemoglobin level (Avram, et al., 2003; Lackson, et al., 2009; Locatelli, et al., 2004; Postorino, et al., 2009). However, correction of anemia to normal hemoglobin level in hemodialysis patients with cardiac disease can increase mortality (Besarab, et al., 1998). Serum phosphorus concentration can be used to assess efficiency of dialysis, medication, and diet. Hyperphosphatemia is associated with increased mortality (Covic, et al., 2009; Lackson, et al., 2009; Trivedi, et al., 2005), but also low phosphate concentration on hemodialysis has been shown to predict premature death (Block, et al., 2004; Kalantar-Zadeh, et al., 2006).

Treatment of hyperphosphatemia with non-calcium-based phosphate binders seems to decrease a risk of death compared with treatment with calcium-based phosphate binders (Jamal, et al., 2013).

Table 4. Mortality risk factors of ESRD patients

Study, year	Country	Patients	Number of patients	Reported predictors of death
Foley, et al., 1997	Canada	Patients with diabetes and ESRD	116	Age, left ventricular hypertrophy, smoking, coronary artery disease, cardiac failure, hypoalbuminemia
Khan, et al., 1993	UK	Incident RRT patients	375	Comorbidity
Lacson, et al., 2009	United States	Hemodialysis patients	78 420	The top 5 actionable variables: serum albumin, phosphorus, hemoglobin, vascular access type, equilibrated Kt/V
Lucas, et al., 2003	Spain	Incident hemodialysis patients	184	Hypertension and comorbidity
Mailloux, et al., 1996	United States	ESRD patients	683	Hypertension, low serum albumin and coronary artery disease
Miskulin, et al., 2003	United States	Incident RRT patients	733	Prevalence and severity of comorbidities
Ono, et al., 2003	Japan	Hemodialysis patients	1010	Ankle-brachial blood pressure index as a sign of peripheral vascular disease
Postorino, et al., 2009	Italy	ESRD patients	537	Low BMI, high waist circumference, age, diabetes, high C reactive protein, and low hemoglobin
Stack, et al., 2002	United States	ESRD patients	2584	Left ventricular hypertrophy
Trivedi, et al., 2005	United States	Peritoneal dialysis patients	191	Phosphorus and lean body mass
van Mannen, et al., 2007	Austria, Italy, Spain, Norway, UK	Incident RRT patients	15 571	Age, diabetes, coronary artery disease, peripheral artery disease, cerebrovascular disease and cancer
Wallen, et al., 2001	United States	ESRD patients	4948	Vascular comorbidity and diabetes increase cardiac mortality

2.3.3 Improvement over time

Survival of patients on RRT has improved over time. In Finland, mortality of the RRT patients decreased between 2002 and 2012 from 106 to 90 deaths / 1000 patient-years (Finnish Registry for Kidney Diseases, Report, 2012). Because the mean age of RRT patients has increased at the same time, age-adjusted mortality has decreased even more. Decrease in mortality is similar in other European countries and in the United States. Two-year adjusted survival in European RRT patients has increased from 79.9% in 2002–2006 to 81.6% in 2005–2009 (ERA-EDTA annual report, 2011), and in the United States adjusted five-year survival among dialysis patients was 30% in 1998 and increased to 36% in 2006, and among patients with kidney transplant, the corresponding survival rates were 81% and 85% (USRDS annual data report, 2013).

The decrease in mortality is probably the result of improvements in RRT and other factors related to disease treatment and public health. However, the knowledge of specific factors behind the improved survival is scarce.

AIMS OF THE STUDY

Survival of patients on RRT is poor, and even worse among RRT patients with diabetes. Nevertheless, knowledge on survival specifically in patients with type 1 diabetes on RRT and factors associating with mortality are scarce and scattered.

The following main aims were addressed in this study:

- To investigate whether survival of patients with type 1 diabetes on RRT has improved over time
- To estimate the association of comorbidities and biochemical variables with survival of patients with type 1 diabetes on RRT
- To examine the changes of medication during predialysis phase and association between medication and survival among patients with type 1 diabetes on RRT

SUBJECTS, STUDY DESIGNS AND METHODS

1. Finnish Registry for Kidney Diseases

This study is based on the data retrieved from the Finnish Registry for Kidney Diseases. This registry has collected information from all nephrology units about dialysis and kidney transplantation patients in Finland since 1964 in collaboration with the EDTA (European Dialysis and Transplantation Association) Registry and as an independent national registry since 1989 still reporting to the EDTA Registry. The Finnish Registry for Kidney Diseases has an estimated coverage of 97–99% of all chronic RRT patients in Finland (Finnish Registry for Kidney Diseases, 2012). The registry is maintained by the Finnish Kidney and Liver Association, and is fully financed by the National Institute of Health and Welfare. The registry collects information on age, sex, cause of ESRD, initial type and changes in type of RRT (peritoneal dialysis, hemodialysis or kidney transplantation), laboratory results, kidney transplantation, and cause of death. Extensive data have been collected since 2000 at start of RRT on the presence of coronary artery disease, peripheral artery disease, left ventricular hypertrophy, heart failure, cerebrovascular disease, and treatment of hypertension and dyslipidemia using a “tick the correct box” system. Kidney disease diagnoses causing ESRD have been stored in the registry according to International Classification of Diseases (ICD) -9, and later as ICD-10 codes. This enables separation between patients with type 1 and type 2 diabetic nephropathy.

All patients provided written informed consent for use of their data anonymously for research purposes, and therefore separate approval of an ethics committee was not needed for this observational study.

2. Study I

In Study I we observed an incident cohort including all patients with type 1 diabetes as the cause of CKD according to the Finnish Registry for Kidney Diseases that had entered chronic RRT in Finland from 1 January 1980 to 31 December 2005 ($n = 1604$). A total of 8719 patients started RRT during this time period and of these, 18.4% had type 1 diabetes as the cause of ESRD. The patients were followed from the first dialysis treatment until death,

recovery of kidney function, moving abroad, lost to follow-up, or the end of the follow-up period (31 December 2007). Recovery of kidney function was recorded in five patients and four patients moved abroad. All patients with chronic glomerulonephritis, except for glomerulonephritis caused by systemic diseases, who had entered RRT during the same time period were included as a control group ($n = 1556$). The patients with chronic glomerulonephritis as the cause of ESRD were chosen to represent a primary renal disease. Thus, we could obtain information to be able to separate the impact of advancement in RRT and diabetic care.

The diagnosis of ESRD was confirmed by kidney biopsy in 80 patients (5%) with type 1 diabetes. This percentage is low because kidney biopsy is considered redundant in patients with type 1 diabetes if there are other signs of microvascular end-organ damage, such as diabetic retinopathy. Kidney biopsy was taken from a minimum of 980 patients (63%) with glomerulonephritis. The biopsy incidence increased over time from 43% to 85%.

The study period was divided into five intervals: 1980–1984, 1985–1989, 1990–1994, 1995–1999, and 2000–2005. The patients were further divided into four groups based on the age at the start of RRT: less than 35 years (444 patients), 35–44 years (586 patients), 45–54 years (383 patients), and 55 years or older (191 patients). Patient survival in each time interval and age group was investigated and compared.

3. Study II

A total of 4421 patients started chronic RRT in Finland from 1 January 2000 to 31 December 2008. According to the Finnish Registry for Kidney Diseases type 1 diabetes was the cause of CKD in 656 (15%) patients, and these were included in Study II. The patients were monitored from the start of RRT until death, recovery of kidney function, loss to follow-up, moving abroad or until the end of the follow-up period (31 December 2008). Recovery of kidney function was recorded in two patients and two patients moved abroad.

Comorbidities were reported at the start of RRT, including peripheral artery disease, coronary artery disease (angina pectoris, myocardial infarction, or coronary artery intervention), cerebrovascular disease, left ventricular hypertrophy, and heart failure. Nephrologists reported the presence of comorbidity at start of RRT using a “tick the correct box” system, and the information on comorbidities were reported according to existing information and not examined for registry purposes. In order to evaluate the difference in the prevalence of

comorbidities between RRT patients with and without diabetes. The control group included all patients 18 years or older with other diseases than type 1 or type 2 diabetes as the cause of CKD starting RRT during the same time period ($n = 2801$). Data on comorbidities was available for 86% (left ventricular hypertrophy) to 96% (coronary artery disease) of the patients with type 1 diabetes, and analyzed the effect of comorbidities on survival.

Age, gender, obesity (BMI categories), and blood pressure in addition to comorbidities, were included into the multivariate analysis. Only 75% of the patients presented of the required all needed information and could be included in the analysis. The possibility of selection bias in adjusted analyses was evaluated by comparison between included and excluded patients.

4. Study III

A total of 5782 patients started chronic RRT in Finland from 1 January 2000 to 31 December 2011. Type 1 diabetes was the cause of CKD in 834 (14%) patients, and these were included in Study III. The patients were monitored from start of RRT until death or the end of the follow-up period (31 December 2011). Recovery of kidney function was recorded in four patients and three patients moved abroad.

Reporting centers are asked to report biochemical variables before RRT start and at the end of each year on RRT, but individual dates of these results are not known. Biochemical values were measured 0–2 weeks before RRT start. Biochemical variables observed in blood or plasma were creatinine, albumin, urea, ionized calcium, phosphorus, hemoglobin, C-reactive protein, total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, triglycerides, and HbA1c. Values were recorded in SI units. Data on biochemical variables were available from 80% (LDL-cholesterol) to 99% (creatinine) of the patients. The association between biochemical variables and survival on RRT was evaluated.

5. Study IV

According to the Finnish Registry for Kidney Diseases 509 patients with type 1 diabetes as the cause of CKD initiated chronic RRT in Finland from 1 January 2000 to 31 December 2006. In Study IV, 496 of these patients who were classified as having type 1 diabetes were also included in the FinDM II study (Sund, et al., 2009). The patients were followed until

death, recovery of renal function, loss to follow-up, moving abroad, or to the end of follow-up (31 December 2009). Recovery of kidney function was recorded in two patients and two patients moved abroad. The FinDM II study has collected information on diabetes patients in Finland from several national health registries including the Finnish Prescription Register maintained by the Social Insurance Institution. That data was used to collect information on medication of these patients.

The Finnish Prescription Register has information on all reimbursed drug purchases for Finnish residents since 1994 (Klaukka, 2001). Drug purchases of these patients was recorded in four-month-periods, because patients can receive medication from a pharmacy for a maximum of three months' use at a time. Observed time intervals were 0 to 4 months, 12 to 16 months, and 32 to 36 months before, and 0 to 4 months after the RRT start. The use of angiotensin-converting enzyme inhibitors (ACEIs), angiotensin II receptor blockers (ARBs), calcium channel blockers (CCBs), beta-blockers (BBs), statins, vitamin D (alfacalcidol, paricalcitol, or dihydrotachysterol), erythropoiesis-stimulating agents (ESAs), and phosphate binders was monitored. Before RRT start, all of the patients using phosphate binders used a calcium-based regimen. After RRT start, six patients began to use a non-calcium-based phosphate binder (sevelamer or lanthanum carbonate). To evaluate the association of medication utilization before RRT start and survival, data on drug purchases during the last four months before RRT start was used.

6. Statistical analyses

Differences in variable distributions between patient groups were assessed using the chi-square test for categorical variables and the Mann-Whitney-U test for continuous variables. Logistic regression was used for adjusted comparison of comorbidity prevalences between patient groups. Median survival times were estimated from the Kaplan-Meier curves, and differences in survival probabilities between groups were assessed using the log-rank test. Relative risks of death as a function of explanatory variables were estimated using Cox proportional hazards regression, with death as the event and censoring at last date of follow-up. Censoring was not performed at time of kidney transplantation. Proportionality assumptions of the Cox regression models were tested by visual inspection of Kaplan-Meier survival curves according to quintiles of laboratory variables. Cox proportional hazards regression was used to perform multivariable modelling of survival probabilities and for

adjustment of potential confounding factors. Two-sided P values lower than 0.05 were considered statistically significant. Interactions between the explanatory variables were considered by including interaction terms in Cox regression model. Interaction means that the effect of one variable on survival differs according to the level of another variable. When analyzing multiple interactions, Bonferroni adjustment was used to calculate reduced significance level for P value in order to decrease risk of detecting interactions simply due to multiple testing, and interaction was considered significant if the two-sided P value was lower than 0.001. For statistical analyses, SPSS Statistics versions 16.0, 17.0, 20.0 and STATA 12.1 were used.

RESULTS

1. Baseline characteristics

Baseline characteristics of the study cohorts are described in Table 5. Median age was 42–45 years at the time of RRT initiation, and two thirds of the patients were male. Hemodialysis and peritoneal dialysis were almost equally often chosen as the first treatment modality. Cardiovascular disease was the cause of death in two thirds of the patients.

Table 5. Baseline characteristics

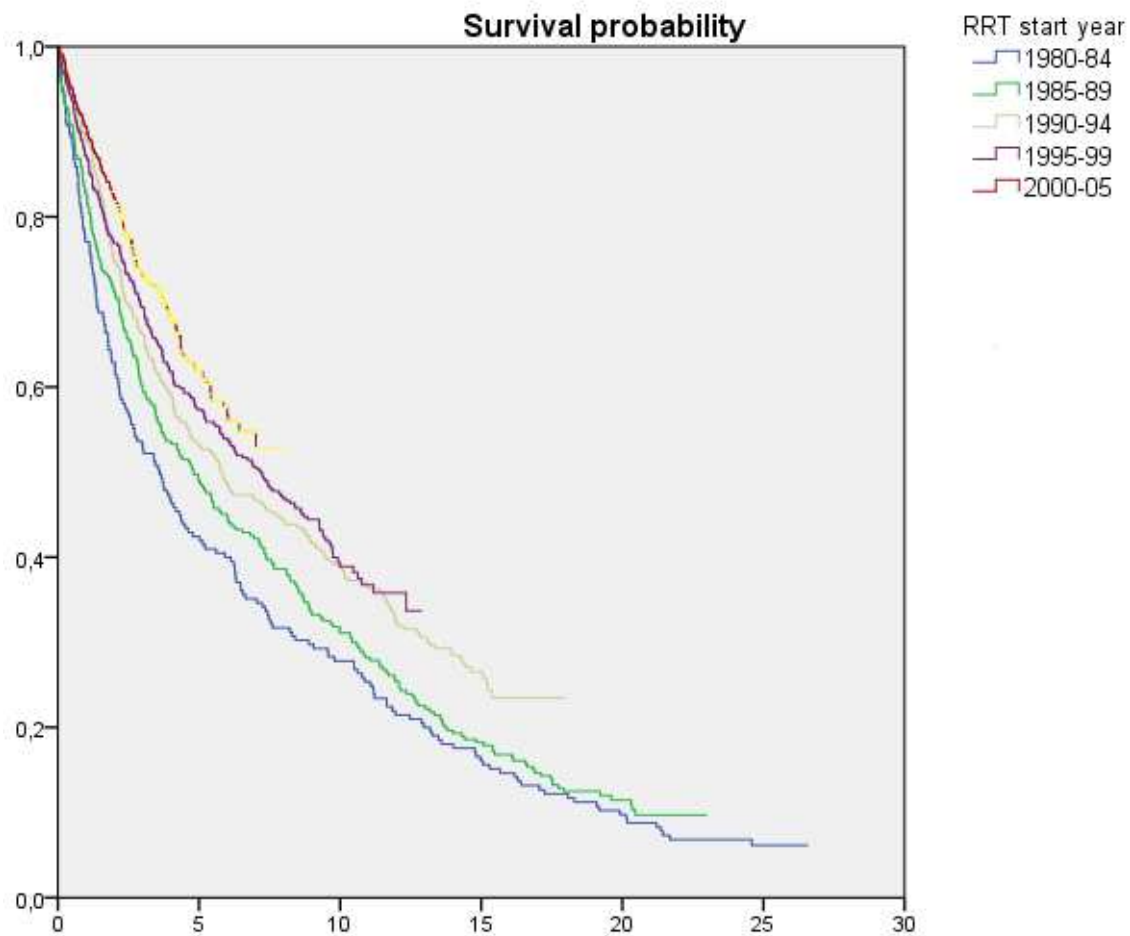
	Study I	Study II	Study III	Study IV
Patients (n)	1604	656	834	496
Median age at RRT start (years)	42.3	44.7	45.7	43.9
Males (%)	63.8	64.3	63.9	64.9
Median follow-up (years)	4.2	2.9	3.7	4.6
Loss to follow-up (n)	4	4	7	4
Primary treatment modality				
-Hemodialysis (%)	46.1	53.2	54.1	52.0
-Peritoneal dialysis (%)	53.5	46.8	45.9	48.0
-Pre-emptive transplantation (%)	0.4	0	0	0
Renal transplantation during follow-up (%)	54.1	39.3	42.6	51.4
Time on dialysis before transplantation (years)	1.3	1.5	1.4	1.4
Cause of death				
-Cardiovascular (%)	65.8	65.9	65.1	68.9
-Infection (%)	17.1	13.6	15.1	13.1

2. Study I: Survival of patients with type 1 diabetes receiving renal replacement therapy in 1980–2007

Survival of patients with type 1 diabetes

Of the 1604 patients with type 1 diabetes, 1047 (65.3%) died during the follow-up. Median survival time increased markedly over time. When RRT started in the periods 1980–1984 and 1995–1999 were compared, median survival time increased from 3.60 years (95% CI 2.50–4.70) to 7.24 years (95% CI 5.74–8.74) (Figure 7). Median survival time of patients starting RRT during 2000–2005 was longer than the maximal follow-up time (8 years), and therefore could not be calculated.

Figure 7. Survival of patients with type 1 diabetes on RRT according to RRT starting periods



Survival improved similarly in all of the age groups. Five-year mortality from the start of RRT decreased from 51% in 1980–1984 to 33% in 2000–2005. The unadjusted relative risk of death decreased 45% when patients that entered RRT in 1980–1984 and 2000–2005 were compared (Table 6). Because age at start of RRT is a significant predictor of survival and median age at start of RRT increased significantly during our study period, corresponding relative risks of death decreased even more in age groups varying between 62% and 69%. Without adjustments, the risk of death increased by 4.1% (95% CI 3.4–4.7%) per year of age at the start of RRT, and hemodialysis as the initial mode of RRT was associated with 1.4-fold risk (95% CI 1.2–1.6) of death compared to peritoneal dialysis. Relative risk of death was significantly higher in patients who did not receive renal transplantation within 2 years from the RRT start compared to those who did (RR 4.0, 95% CI 3.5–4.6). Gender was not associated with risk of death.

Adjusted survival of patients with type 1 diabetes

When adjusted for age and sex, survival improved more prominently, with relative risk of death of 0.33 for patients with type 1 diabetes entering RRT in 2000–2005 compared to 1980–1984. When initial mode of dialysis and having or not having received a kidney transplant within 2 years from the start of RRT were added in to a multivariate model, the relative risk of death decreased even more markedly to 0.23 (Table 6). Decrease in the relative risk of death was similar in patients who received a kidney transplant (RR 0.20, 95% CI 0.11–0.37) and in those who did not (RR 0.25, 95% CI 0.19–0.33).

Table 6. Survival according to the start period of renal replacement therapy among patients with type 1 diabetes and patients with glomerulonephritis

Type 1 diabetes	1980–1984	1985–1989	1990–1994	1995–1999	2000–2005
5-year survival (%)	49	55	59	62	67
Unadjusted RR	1	0.87	0.70	0.66	0.55
(95% CI)		(0.72–1.06)	(0.58–0.85)	(0.54–0.81)	(0.44–0.68)
Adjusted RR ^a	1	0.72	0.53	0.43	0.33
(95% CI)		(0.59–0.87)	(0.44–0.65)	(0.35–0.52)	(0.26–0.41)
Adjusted RR ^b	1	0.64	0.44	0.33	0.23
(95% CI)		(0.52–0.77)	(0.36–0.54)	(0.27–0.41)	(0.19–0.29)
Glomerulonephritis	1980–1984	1985–1989	1990–1994	1995–1999	2000–2005
5-year survival (%)	77	75	67	69	77
Unadjusted RR	1	1.01	1.21	1.17	0.88
(95% CI)		(0.82–1.25)	(0.98–1.50)	(0.93–1.46)	(0.68–1.14)
Adjusted RR ^a	1	0.86	0.72	0.59	0.37
(95% CI)		(0.69–1.06)	(0.58–0.90)	(0.47–0.74)	(0.28–0.49)
Adjusted RR ^b	1	0.76	0.60	0.49	0.30
(95% CI)		(0.61–0.94)	(0.48–0.75)	(0.38–0.62)	(0.23–0.40)

RR, Relative risk of death; 95% CI, 95% Confidence interval

^aAdjusted for age at start of RRT and sex

^bAdjusted for age at start of RRT, sex, initial mode of dialysis, and having or not having received a kidney transplant within two years of the RRT start

Comparison between patients with type 1 diabetes and glomerulonephritis

There were 823 (52.9%) deaths among patients with glomerulonephritis, and 733 patients were censored. Of the censored patients, 719 were alive on 31 December 2007, eight regained own kidney function, four moved abroad, and two were lost to follow-up. Hemodialysis was the initial RRT mode in 64.8%, peritoneal dialysis in 33.9%, and pre-emptive kidney transplantation in 1.2% of the patients. The patients with glomerulonephritis had significantly higher median survival time than that of patients with type 1 diabetes. However, it did not increase significantly during the follow-up (median survival time was 11.50 years). The unadjusted relative risk of death (RR = 0.88) improved markedly after adjustment for other

variables (RR = 0.30) in patients entering RRT in 2000–2005 compared to 1980–1984 (Table 6). Interaction analysis between ESRD diagnosis (type 1 diabetes and glomerulonephritis) and the RRT start period with adjustment for age, gender, treatment mode, and kidney transplant status at 2 years indicated a greater decrease in the risk of death among patients with type 1 diabetes than patients with glomerulonephritis ($P = 0.007$). The risk of death for patients with type 1 diabetes compared to patients with glomerulonephritis on RRT was 3.5-fold during 1980–1984, but decreased to 2.7-fold during 2000–2005.

Interaction analysis

There were no statistically significant first or second degree interactions in patients with type 1 diabetes between the variables RRT start period, age at start of RRT, gender, initial mode of dialysis, and having or having not received a kidney transplant within 2 years from the RRT start.

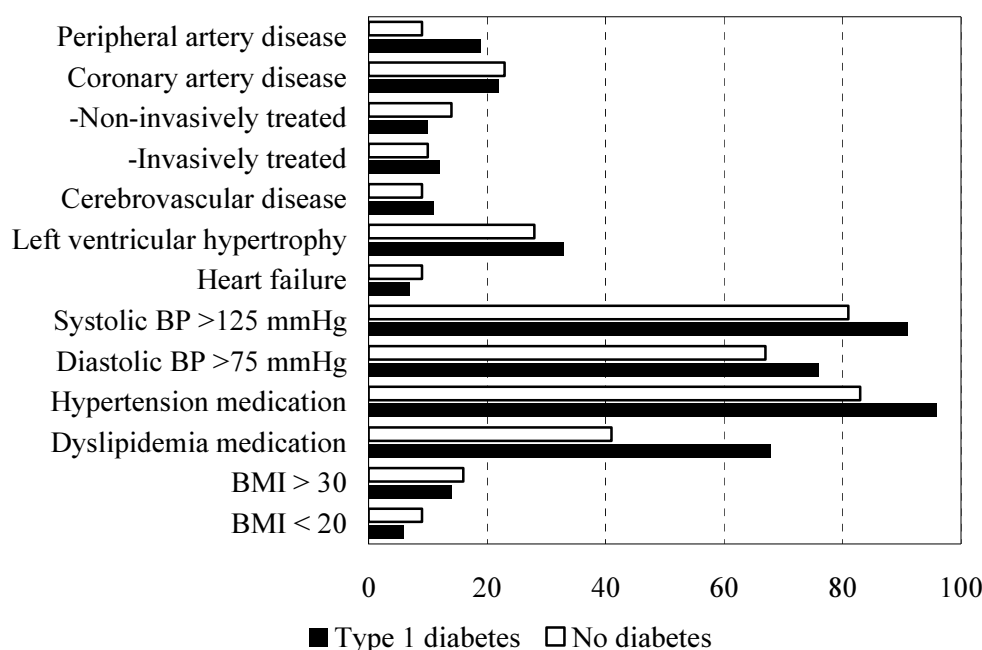
3. Study II: Comorbidities and survival of patients with type 1 diabetes on renal replacement therapy

Prevalence of comorbidities, obesity, and medication for hypertension and dyslipidemia

Patients with type 1 diabetes had high prevalence of comorbidities with an average of 1.2 comorbidity per patient, and 52% of the patients had at least one comorbidity. The most common comorbidities were left ventricular hypertrophy, coronary artery disease, and peripheral artery disease (Figure 8).

Comorbidities, especially peripheral artery disease, were more common in patients with type 1 diabetes than in patients without diabetes, and patients with type 1 diabetes more often used medication for dyslipidemia and hypertension. The mean age at RRT start was 15 years lower among the patients with type 1 diabetes, and therefore after adjustment for age and sex the probability for having a comorbidity or medication (Figure 8) was significantly higher ($P < 0.05$) in all observed variables except for diastolic blood pressure and obesity.

Figure 8. Prevalence of comorbidities in patients with type 1 diabetes on RRT



Effect of comorbidities on risk of death

Of the patients, 209 died during follow-up. All observed comorbidities were associated with increased risk of death in a univariate model. After adjustment for age and sex, heart failure was associated with the highest risk of death, but the association of invasively treated coronary artery disease and high diastolic blood pressure with survival disappeared (Table 7). When all variables listed in Table 4 were analyzed in the multivariate model, independent predictors of death were age at start of RRT, peripheral artery disease, left ventricular hypertrophy, and heart failure.

The information on comorbidities was incomplete for 24.7% of the patients with type 1 diabetes, and these patients were excluded from the multivariate analysis. Survival between included and excluded patients was, however, similar. Furthermore, addition of initial treatment modality into the multivariate model did not change the results.

Number of comorbidities and risk of death

Increasing the number of comorbidities increased the risk of death. After adjustment for age and sex, the patients with more than two comorbidities, compared to the patients without comorbidities, had a 3.6-fold risk of death (Table 8). Median survival time was 7.0 years with one, 4.4 years with two, and 2.7 years with three or more comorbidities. The median survival time was over 9 years if there was no comorbidity (Figure 9).

Table 7. Effect of comorbidities on risk of death among patients with type 1 diabetes on RRT

	Unadjusted RR (95% CI)	Adjusted ^a RR (95% CI)	Adjusted ^b RR (95% CI)
Heart failure	4.87 (3.21–7.38)	3.25 (2.10–5.03)	2.50 (1.32–4.59)
Peripheral vascular disease	2.92 (2.16–3.94)	2.31 (1.69–3.14)	1.88 (1.25–2.83)
Left ventricular hypertrophy	1.75 (1.29–2.38)	1.76 (1.30–2.39)	1.68 (1.18–2.40)
Age at start (per 10-year increment)	1.62 (1.43–1.85)	1.63 (1.43–1.85)	1.41 (1.15–1.72)
Coronary artery disease			
-No disease	1	1	1
-Non-invasively treated	2.09 (1.42–3.07)	1.63 (1.10–2.42)	1.32 (0.78–2.22)
-Invasively treated	1.56 (1.05–2.30)	1.01 (0.67–1.52)	0.65 (0.37–1.14)
Cerebrovascular disease	2.18 (1.51–2.30)	1.63 (1.11–2.38)	1.25 (0.76–2.05)
Body mass index			
-20–30	1	1	1
-<20	1.67 (1.00–2.79)	1.56 (0.93–2.62)	1.59 (0.84–3.00)
->30	1.02 (0.66–1.55)	0.92 (0.60–1.40)	0.82 (0.49–1.36)
Female gender	1.07 (0.81–1.43)	1.15 (0.86–1.52)	1.29 (0.91–1.84)
Systolic blood pressure (per 10 mmHg)	0.98 (0.93–1.04)	0.99 (0.94–1.05)	0.98 (0.89–1.08)
Diastolic blood pressure (per 10 mmHg)	0.85 (0.76–0.95)	1.00 (0.89–1.13)	1.02 (0.84–1.24)

RR, relative risk of death; 95% CI, 95% confidence interval

^a Age- and sex-adjusted^b Multivariate model of all variables**Table 8.** Number of comorbidities and risk of death among patients with type 1 diabetes on RRT

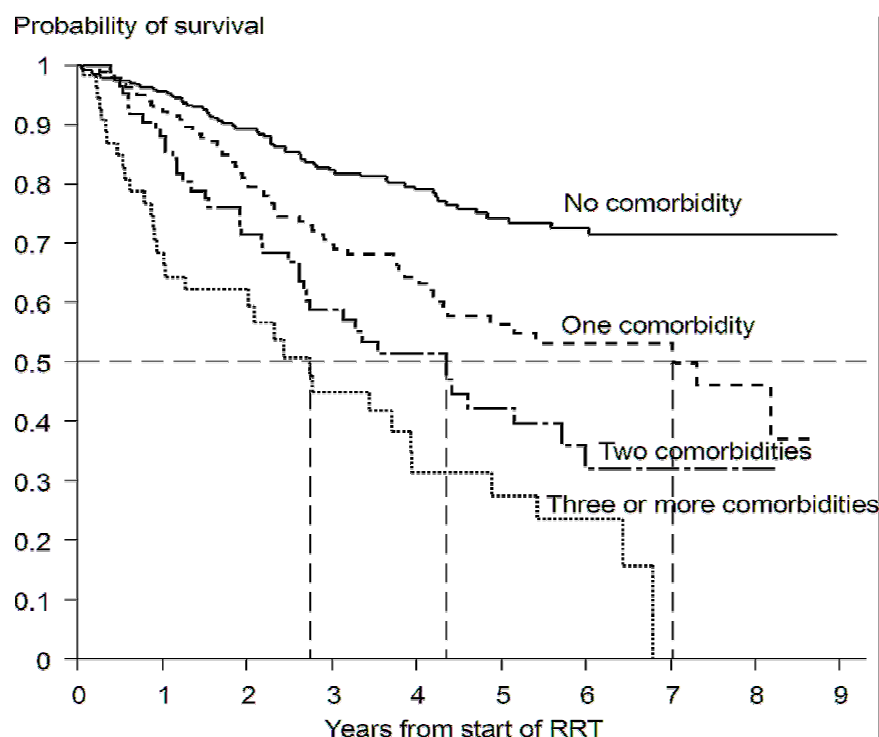
Number of comorbidities	Unadjusted RR (95% CI)	Adjusted ^a RR (95% CI)
0	1	1
1	1.96 (1.38–2.79)	1.78 (1.25–2.54)
2	3.05 (2.05–4.53)	2.40 (1.59–3.62)
3 or more	5.18 (3.38–7.93)	3.65 (2.33–5.70)

RR, relative risk of death; 95% CI, 95% confidence interval

^a Age-, and sex-adjusted

The risk of death was 39% after five years on RRT for all patients with type 1 diabetes, but only 26% in those without comorbidities. Hereby, the population-attributable risk was 33% $[(0.39-0.26)/0.39]$. It indicates that one third of the deaths could be attributed to comorbidities. The estimate was similar after adjustment for age and sex.

Figure 9. Survival probability of patients with type 1 diabetes starting RRT according to number of comorbidities.



Interaction analysis

No statistically significant interactions were observed between comorbidities, blood pressure, BMI, sex, and age at start of RRT.

4. Study III: Biochemical variables and survival of patients with type 1 diabetes on renal replacement therapy

Association of biochemical variables and survival

Of the patients, 313 died during follow-up. When we analyzed association of biochemical variables and mortality without adjustment, significant predictors of worse survival were lower creatinine and albumin and increased C-reactive protein concentrations. When adjusted for age and sex, low hemoglobin was also associated with higher mortality in addition to the above-mentioned variables (Table 9). Of the patients, 82% used erythropoiesis-stimulating agents. The use of erythropoiesis-stimulating agents did not have an effect on relative risk of death associated with hemoglobin concentration.

Table 9. Biochemical variables before entering RRT and associated risks of death in patients with type 1 diabetes on RRT

	Median value	Unadjusted RR	Unadjusted 95% CI	Adjusted ^a RR	Adjusted ^a 95% CI
Creatinine (per 100 umol/l)	558	0.86 ^c	0.81–0.91	0.88 ^c	0.83–0.94
Albumin (per 5 g/l)	32.0	0.84 ^c	0.77–0.91	0.79 ^c	0.73–0.87
Hemoglobin (per 10 g/l)	109	0.94	0.88–1.01	0.93 ^b	0.86–1.00
C-reactive protein (per 10 mg/l)	5.0	1.04 ^b	1.01–1.07	1.04 ^b	1.01–1.07
HbA1C (%)	8.3	1.04	0.97–1.11	1.07	1.00–1.15
Phosphorus (mmol/l)	1.84	0.89	0.73–1.09	1.03	0.83–1.27
Urea (per 10 mmol/l)	27.1	1.09	0.95–1.24	1.01	0.88–1.16
Calcium-ion (mmol/l)	1.16	0.70	0.26–1.86	0.45	0.17–1.22
Cholesterol (mmol/l)	4.15	0.91	0.82–1.02	0.94	0.84–1.04
HDL-cholesterol (mmol/l)	1.22	0.87	0.67–1.13	0.78	0.59–1.03
Triglycerides (mmol/l)	1.43	0.92	0.80–1.06	0.94	0.82–1.09
LDL-cholesterol (mmol/l)	2.09	0.91	0.80–1.05	0.96	0.84–1.10

RR, relative risk of death per one unit increase of value; 95% CI, 95% confidence interval

^aAge- and sex-adjusted

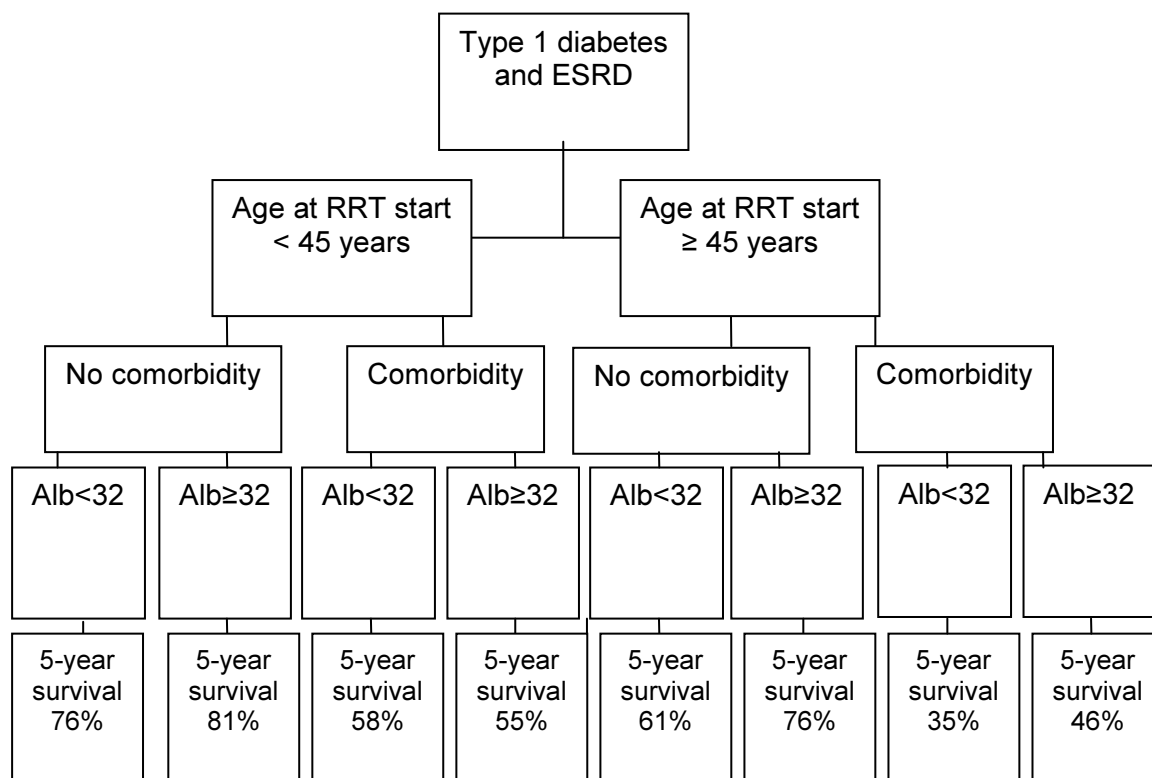
^b $P < 0.05$

^c $P < 0.001$

Because comorbidities are significant predictors of death, and may associate with biochemical values and their medical treatment, a multivariate adjustment for comorbidities (coronary artery disease, peripheral vascular disease, left ventricular hypertrophy, heart failure and cerebrovascular disease), age, sex, and initial treatment modality of RRT was performed. After this adjustment, independent predictors of mortality were lower creatinine, and albumin, and increased C-reactive protein.

Figure 10 shows how categorizing by age at RRT start, presence of comorbidity, and predialytic albumin level helps to detect patients with high risk of death.

Figure 10. Effect of age at RRT start, comorbidity status, and albumin level on survival



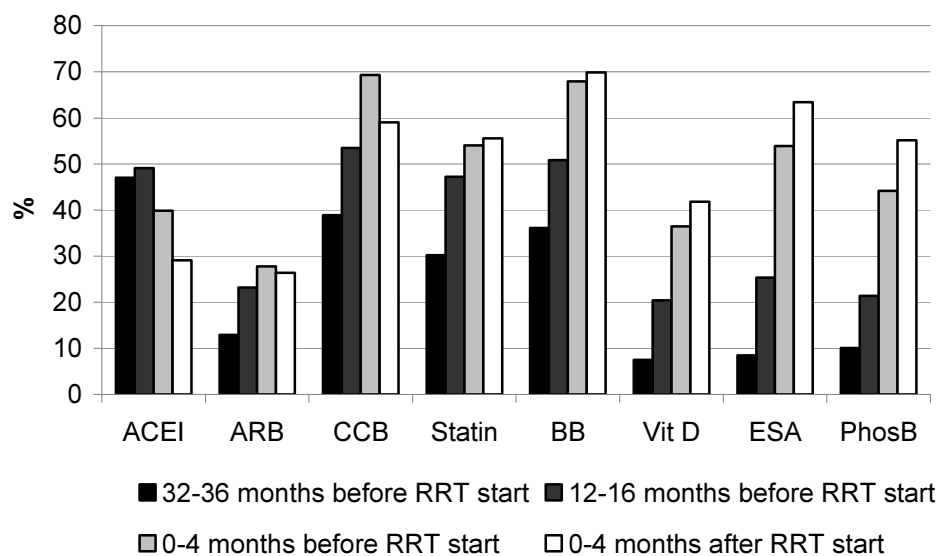
Alb, albumin (g/l) measured 0–2 weeks before RRT start

5. Study IV: Medication during predialysis phase and survival of patients with type 1 diabetes on renal replacement therapy

Prevalence of medication

Of the 496 patients, the most frequently used medications before RRT start were CCBs (69%), BBs (68%), and ACEIs or ARBs (63%). Predialytic use of all groups of medication became more common when start of RRT was approaching except for ACEIs (Figure 11). After initiation of RRT, use of other than antihypertensive medication increased. Patients with cardiovascular comorbidities more often used statins, BBs, and vitamin D, whereas the utilization of CCBs was less frequent in patients with cardiac problems (Table 10). Higher concentrations of serum albumin were associated with the use of vitamin D and/or phosphate binders.

Figure 11. Prevalence of drug utilization



Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CCB, calcium channel blocker; BB, beta-blocker; Vit D, vitamin D; ESA, erythropoiesis-stimulating agent; PhosB, phosphate binder

Table 10. Patient characteristics and drug utilization 0 to 4 months before RRT start

	Use of drug	Number of patients	Male (%)	PAD (%)	CAD (%)	HF (%)	CVD (%)	LVH (%)
ACEI	yes	195	61.5	12.1	20.1	4.1	9.9	27.3
	no	301	67.1	23.0	21.4	6.4	10.0	31.3
ARB	yes	138	65.9	19.5	20.9	7.0	6.3	29.4
	no	358	64.5	18.5	20.7	5.0	11.3	29.8
CCB	yes	344	67.4	16.6	18.3	3.2	10.0	29.5
	no	152	59.2	18.3	26.7	10.7	9.9	30.2
Statin	yes	268	65.3	24.1	29.3	5.7	11.9	33.0
	no	228	64.5	12.3	10.7	5.4	7.7	25.8
BB	yes	337	67.4	19.6	24.8	6.6	10.3	32.3
	no	159	59.7	17.1	12.8	3.4	9.2	24.5
Vitamin D	yes	181	64.1	19.2	26.7	6.1	10.1	28.3
	no	315	65.4	18.5	17.5	5.3	9.9	30.6
ESA	yes	267	58.8	20.6	18.8	6.2	10.8	25.4
	no	229	72.1	16.7	23.3	4.8	8.9	34.7
PhosB	yes	219	65.8	17.9	22.1	6.4	6.4	27.2
	no	277	64.3	19.5	19.9	4.9	12.7	31.8
All		496	64.9	18.8	20.9	5.6	10.0	29.7

	Use of drug	Number of patients	Age at RRT start (years)	BMI (kg/m ²)	Syst BP (mmHg)	Albumin (g/l)
ACEI	yes	195	43.2	24.0	155	32.0
	no	301	44.4	24.5	156	32.0
ARB	yes	138	43.3	24.5	160	32.0
	no	358	44.1	24.2	154	32.0
CCB	yes	344	44.3	24.5	158	32.0
	no	152	42.6	24.1	150	31.0
Statin	yes	268	45.9	24.9	156	32.0
	no	228	41.3	23.7	156	31.3
BB	yes	337	44.7	24.8	157	32.0
	no	159	42.3	23.6	151	31.0
Vitamin D	yes	181	47.4	23.8	153	33.0
	no	315	42.3	24.5	157	31.5
ESA	yes	267	44.9	23.7	156	32.0
	no	229	42.8	24.9	155	32.0
PhosB	yes	219	44.8	24.6	158	33.0
	no	277	43.2	24.3	150	31.0
All		496	43.9	24.4	156	32.0

PAD, peripheral artery disease; CAD, coronary artery disease; HF, heart failure; CVD, cerebrovascular disease; LVH, left ventricular hypertrophy; Syst BP, systolic blood pressure; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CCB, calcium channel blocker; BB, beta-blocker; ESA, erythropoiesis-stimulating agent; PhosB, phosphate binder; All, values for all of the patients

Median values are reported for continuous variables

Bolded, statistically significant difference ($P < 0.05$)

Association between medication and intermediate markers

Ninety percent (N=445) of the patients used antihypertensive medication before RRT start. Median systolic blood pressure was 156 mmHg and diastolic blood pressure 85 mmHg in patients with antihypertensive medication compared with 145 mmHg and 87 mmHg, respectively, in patients without antihypertensive medication. Hemoglobin level was higher among users of ESAs (113 vs. 105 g/l, $P<0.001$), and low density lipoprotein (LDL) cholesterol concentration was lower among statin users, although without statistical significance (2.07 vs. 2.29 mmol/l, $P=0.07$). Use of vitamin D was not associated with ionized calcium (1.17 vs. 1.17 mmol/l, $P=0.57$) or phosphate (1.80 vs. 1.85 mmol/l, $P=0.22$) concentration. Concentration of ionized calcium was higher among users of phosphate binders (1.18 vs. 1.16 mmol/l, $P=0.002$), but, surprisingly, the use of phosphate binders did not associate with phosphate concentration (1.80 vs. 1.86 mmol/l, $P=0.20$).

When exploring these associations after adjustment for age, gender, albumin, systolic blood pressure, body mass index (BMI), and comorbidities, the use of ESAs correlated with higher hemoglobin concentration. However, systolic or diastolic blood pressure between users and non-users of antihypertensive drugs, phosphate concentration between users and non-users of phosphate binders, and LDL-cholesterol concentration between statin users and non-users did not differ significantly.

Association between medication and survival

Of the patients, 206 died during follow-up. When evaluated without adjustment, the use of CCBs during four months before the start of RRT was the only medication associating with survival, and showed 29% reduction in risk of death. The results for use of CCBs remained unchanged after adjustment for age and sex. Moreover, the use of vitamin D was associated with a 30% decrease in the risk of death (Table 11).

After adjustment for age, sex, comorbidities (coronary artery disease, peripheral artery disease, left ventricular hypertrophy, heart failure, and cerebrovascular disease), body mass index, and serum albumin, no associations were found between the use of medication and mortality (Table 12). When analyzing separately in patients with and without comorbidities as subgroups, or if the use of ACEIs and ARBs were combined, the results remained similar. Adding information on renal transplantation status did not have an effect on the results either. The association of medication use 0 to 4 months after RRT start and survival in this multivariate model was also assessed. Better survival was associated with the use of vitamin

D (RR 0.63, 95% CI 0.44–0.92). Otherwise the results were similar to those reported regarding medicine use before RRT start.

Table 11. Medication before RRT start and relative risk of death

	Unadjusted		Age- and sex-adjusted	
	RR	95% CI	RR	95% CI
Antihypertensive drug	0.79	0.51–1.23	0.78	0.50–1.21
-ACEI	0.79	0.59–1.05	0.79	0.59–1.05
-ARB	0.98	0.72–1.34	0.98	0.72–1.33
-CCB	0.71	0.54–0.95	0.71	0.53–0.95
-BB	1.01	0.76–1.36	0.99	0.75–1.34
Statin	1.14	0.86–1.50	0.97	0.73–1.28
Vitamin D	0.82	0.61–1.09	0.70	0.52–0.94
Erythropoietin	0.93	0.70–1.22	0.86	0.65–1.14
Phosphate binder	0.82	0.62–1.08	0.82	0.62–1.08

Drug utilization was recorded if patient purchased drug 0 to 4 months before start of RRT

Antihypertensive drug = use of ACEI, ARB, CCB, and/or beta-blocker

RR, relative risk of death; 95% CI, 95% confidence interval

Bolded, $P < 0.05$

Table 12. Medication and risk of death after multivariable adjustment

	RR	CI 95%
Antihypertensive drug	1.02	0.60–1.73
-ACEI	0.91	0.65–1.28
-ARB	1.16	0.81–1.65
-CCB	0.91	0.64–1.30
-BB	1.01	0.71–1.44
Statin	0.95	0.67–1.34
Vitamin D	0.88	0.63–1.24
Erythropoietin	0.93	0.66–1.31
Phosphate binder	1.10	0.79–1.53

Drug utilization was recorded if patient purchased drug 0 to 4 months before start of RRT

Relative risk of death was adjusted in multivariate model for age, sex, coronary artery disease, peripheral artery disease, left ventricular hypertrophy, heart failure, cerebrovascular disease, body mass index, and serum albumin

Antihypertensive drug = use of ACEI, ARB, CCB, and/or BB

RR, relative risk of death; 95% CI, 95% confidence interval

DISCUSSION

1. Results from this study

Improved survival

In Study I we showed a considerably improved survival of patients with type 1 diabetes on RRT throughout the follow-up period 1980–2007. It is worth noting that survival improved despite the increasing median age at start of RRT, and the declining probability to receive a kidney transplant. These transitions should change the prognosis in an unfavorable direction. However, patients' age at the time of type 1 diabetes diagnosis has not changed, but the time from diagnosis to ESRD has increased (Finne, et al., 2005). When the patients with glomerulonephritis as the cause of CKD, excluding patients with systemic disease, were compared to the patients with type 1 diabetes, a more substantial survival benefit over time was found for diabetes patients. This indicates advances in diabetes care and management of diabetic complications in addition to developments in overall management of the patients with chronic renal disease.

During the study period, management of diabetes has developed markedly. New insulin regimens have been developed and multiple insulin injections have led to more stable blood glucose control. Blood glucose measurements at home have become mainstay, and follow-up of glycosylated hemoglobin has enabled better long-term glucose control. These improvements most likely explain part of the observed improvement of survival in this study. On the other hand, dialysis therapy has also improved over the years. At the beginning of this study period hemodialysis patients were treated with low-flux hemodialysis, but during the last decades hemodiafiltration and modern high-flux dialyzers with better biocompatibility have become available enhancing better uremic toxin clearance and flexibility of hemodialysis treatment. Furthermore, the weekly hemodialysis time has increased. In this study of patients with type 1 diabetes, the mean number of weekly hemodialysis treatment hours increased from 11.4 (95% CI 10.9–12.0) in 1992 to 13.5 (95% CI 12.8–14.2) in 2007. On peritoneal dialysis therapy the improvement of fluids with better tolerability, solute removal, and ultrafiltration capability have increased efficacy. In addition, the use of automated overnight peritoneal dialysis machines has increased, leading to greater toxin clearance, better adjustment of peritoneal dialysis to everyday life with improved compliance

to therapy, and possibly to a decrease in peritonitis episodes (Nessim, et al., 2009; Rabindranath, et al., 2007). The use of an automated machine as an initial peritoneal dialysis treatment rose from 2% in 1992 to 27% in 2007 in this study population. Since better uremic toxin clearance improves survival in patients on dialysis (National Kidney Foundation, 2006), the improvement of dialysis techniques and increase in dialysis dose could have led to improved survival in this study population.

This study indicates that both management of type 1 diabetes and development in RRT have led to improved survival of these patients.

Comorbidities and survival

In Study II comorbidities were shown to be common among patients with type 1 diabetes at the time that they entered RRT during 2000–2008 in Finland, and these comorbidities correlate with increased risk of death. All observed comorbidities associated with lower probability of survival, and after adjustment for confounding factors, peripheral artery disease, left ventricular hypertrophy, and heart failure remained independent predictors of death. The risk of death increased with growing number of comorbidities, and patients with one or more comorbidities compared to patients without comorbidities had more than twofold risk of death. Moreover, the prevalence of comorbidities, particularly peripheral artery disease, was higher in patients with type 1 diabetes compared to patients without diabetes on RRT.

No information about severity or underlying cause of comorbidities was available. This makes it more challenging to estimate the role of comorbidities to mortality. Heart failure was associated with the highest increase in the risk of death. Patients with heart failure without ESRD have poor prognosis (Harjola, et al., 2010; Salpeter, et al., 2012), and it is not surprising that combination of these two severe conditions predict low life expectancy. Another strong independent predictor of death was peripheral artery disease, which often causes infectious problems to the patients. No information about the presence of infections was available, but infection was not a more common cause of death among patients with peripheral artery disease than without. However, infections may have potentiated the risk of death among patients with peripheral artery disease. Patients with peripheral artery disease often also have vascular disease in heart and brain, which could increase mortality. Of the comorbidities, left ventricular hypertrophy was the most common independent predictor of death with prevalence in one third of the patients. Therefore it is important to identify and treat early factors that lead to left ventricular hypertrophy, such as hypertension. The prevalence of prescribed blood pressure-lowering drugs was high, but most of the patients had

hypertension prior to start of RRT. However, monitored blood pressure was a single observation, and may not represent long-term blood pressure level. Because blood pressure was measured just before RRT start, fluid retention can cause elevation of blood pressure.

Biochemical variables and survival

In Study III, before start of chronic RRT, independent predictors of death among patients with type 1 diabetes included lower creatinine and albumin, and increased C-reactive protein. Low hemoglobin was also associated with poor survival. However, the prevalence of comorbidities was higher among patients with low hemoglobin concentration and may explain this result.

Creatinine and albumin can be used to assess nutritional status, and malnutrition often correlates with more severe comorbidity and mortality. Creatinine concentration also reflects muscle mass and low creatinine associates with frailty and general morbidity. Other causes of hypoalbuminemia are substantial proteinuria, impaired food absorption, and liver malfunction. Therefore our results suggest that improvement of nutritional status and treatment of other possible causes of hypoalbuminemia might reduce mortality. Diagnosis and efficient treatment of ongoing inflammatory process also seems to be important.

Medication during predialysis phase and survival

In Study IV, in patients with type 1 diabetes, the use of medication becomes more frequent during the predialysis phase of renal disease. Before RRT start, over half of these patients use ACEIs or ARBs, CCBs, statins, BBs, or ESAs. Although after adjustment for age and sex there was an association between the utilization of CCBs or vitamin D before RRT start and lower mortality, the association disappeared after further adjustment for confounding factors. Survival prognosis appears similar among patients with and without medication.

Results confirmed that the use of medication is abundant in patients with type 1 diabetes during predialytic stage of renal disease. Still, the evidence on the effect of specific medication on survival is scarce in all ESRD patients and almost nonexistent in patients with type 1 diabetes. The use of antihypertensive medication becomes more frequent during the predialysis phase, and the use of ACEIs shifts to the use of CCBs, probably because of increase in potassium and creatinine concentrations. Despite the abundant use of antihypertensive medication, blood pressure was high among these patients. Because BBs block the activated adrenergic system in CKD and cardiovascular mortality is high in ESRD patients, the use of BBs could be beneficial for these patients. There are, however, factors that limit the use of BBs: fear of hypotension and bradycardia, suppressed sensation of

hypoglycemia in patients with diabetes, and lack of research evidence. Because CCBs do not dialyze or excrete through kidneys and hereby dosing needs no alterations in CKD, they are commonly used for hypertension and angina pectoris in ESRD patients. ACEIs and ARBs are recommended during the predialysis phase in patients with diabetes as they slow down the progression of diabetic nephropathy and albuminuria (Brenner, et al., 2001; Kshirsagar, et al., 2000; Lewis, et al., 2001). Because cardiovascular morbidity and mortality is high among these patients, the use of statins seems justifiable. The use of statins is frequent and LDL-cholesterol levels are acceptable. However, the observed increase in the use of statins during the last three years before RRT initiation, raises the question whether more aggressive treatment of hyperlipidemia at earlier stages of diabetic nephropathy would decrease morbidity and mortality on cardiovascular disease. CKD disturbs vitamin D and bone metabolism, and this accelerates arterial calcification. A significant association was found for the use of vitamin D after RRT start and lower mortality, and therefore correction of vitamin D deficiency may be beneficial for these patients. Due to confounding by indication it is difficult to assess effects of medication in an observational study. However, a very large beneficial or adverse effect on survival does not appear likely for any of the drugs investigated. Use of medication seems to keep patients in most cases on a comparable survival level to patients not on the same medication.

2. Strengths and weaknesses

Knowledge on survival and the impact of factors affecting survival among patients with type 1 diabetes on RRT is scarce and scattered. This study thus provides novel information. The major strengths of these studies include the virtually complete coverage of patients with type 1 diabetes entering RRT during the entire study periods in Finland, adequate number of patients, sufficiently long follow-up periods, and complete information on the outcome. This reduces the possibility of selection bias. Furthermore, few earlier studies have been able to distinguish between patients with type 1 and type 2 diabetes. Data on comorbidities were exceptionally comprehensive and collected systematically using the same form for all patients, which reduces information bias. Potential influence of noncompliance could be partly overcome, because the information on the use of medication was based on reimbursed medicine purchases instead of reported prescriptions.

There are also some limitations in these studies. Firstly, they are observational. Therefore, no definitive conclusion can be made that the associations between the observed variables and survival are causal. This problem was addressed by adjusting for a large number of potential confounders. Unfortunately, for these adjustments there was no information on the severity of the comorbidities, and severity may well correlate with both studied factors and mortality and thus confound results. More reliable causal inferences could be made in randomized intervention trials. However, in the absence of randomized trials an observational cohort study gives the best evidence to evaluate the factors affecting survival and allows assessment of multiple potential factors in the same study. Secondly, the data on biochemical variables and comorbidities were unavailable for some of the patients, which reduced the proportion of the patients included in the multivariate analyses. This potential selection bias was estimated by comparing survival of patients included and excluded in these analyses. Thirdly, the results may not be valid in other parts of the world, as the Finnish population is almost entirely white, genetically quite homogenous, and the incidence of type 1 diabetes in Finland is one of the highest in the world (Karvonen, et al., 2000). Therefore, special attention has been directed towards treatment of type 1 diabetes, and that may have led to the favourable progress in prognosis of the Finnish patients with type 1 diabetes (Asao, et al., 2003). Potential pitfalls of these studies also include the differences in the characteristics of the patients with and without an indication to use a medication, and potential reporting bias towards more difficult cases of the comorbidities, as the information on comorbidities were reported according to existing information and not examined for registry purposes. For example, the low prevalence of coronary artery disease compared with an earlier study (Vilar, et al., 2007) may indicate underreporting of comorbidities.

Cox proportional hazards regression models were used for adjustment of confounding factors. There are limitations in the use of this analysis method, because it assumes a linear relationship between the explanatory variable and the logarithm of the hazard ratio. It furthermore assumes that hazard ratio related to the predictive variable remains stable during time of follow-up. However, increased risk of death might be associated, for example, to both low and high hemoglobin values while the risk is the lowest in the middle range. Therefore, the explanatory variables were also explained as categories to detect these problems. Change in hazard ratio of death over time can be estimated by visual inspection of Kaplan-Meier curves. If there was significant change, Cox proportional hazards model could not be applied to this variable, for example, if male gender would predict increased mortality during the first year of follow-up, but female gender after two years.

3. Comparison to previous results

The results presented here of the improved prognosis are in line with previous observations from studies exploring survival of patients with diabetes and ESRD (Sørensen, et al., 2007; van Dijk, et al., 2005), although Villar, et al. (2007) found no improvement in the prognosis of patients with type 1 diabetes on RRT 1991–2005. However, this study is the first to focus only on patients with type 1 diabetes and expanding the observation period to almost three decades.

Several studies have shown that comorbidities are more common among patients with diabetes than among other RRT patients (Lok, et al., 2004; Stel, et al., 2005; Villar, et al., 2007). The study by Villar and colleagues also reported the prevalence of comorbidities separately for patients with type 1 diabetes in New Zealand and Australia 1991–2005. They found markedly higher prevalence of coronary artery disease and peripheral artery disease than reported here. Age at start of RRT was approximately the same in both studies, and does not explain the observed differences. Therefore, the difference may arise from the unequal reporting systems or differences in the patients.

It is a well reported fact that comorbidities increase mortality among RRT patients (Khan, et al., 1993; Miskulin, et al., 2003; Stack, et al., 2002; van Mannen, et al., 2007). There are only two small studies that have been reported on patients with diabetes on RRT estimating the effect of comorbidities on mortality (Foley, et al., 1997; Racki, et al., 2007). These studies reported increased mortality associating with heart failure, left ventricular hypertrophy, and coronary artery disease. However, no study has focused separately on patients with type 1 diabetes.

Among patients with type 1 diabetes but without ESRD, predictors of death include hyperglycemia (Rossing, et al., 1996; Shankar, et al., 2007) and hypercholesterolemia (Soedamah-Muthu, 2008). Hyperglycemia is associated with poor survival, also in patients with diabetes and ESRD (Ishimura, et al., 2009; Morioka, et al., 2001; Smavatkul, et al., 2007; Williams, et al., 2010), but evidence of the association with hypercholesterolemia is lacking (Foley, et al., 1997; Morioka, et al., 2001; Smavatkul, et al., 2007). These results are in line with our findings. Patients with diabetes on RRT are special also compared to other patients on RRT. Among ESRD patients, worse survival is in general shown to associate with

hyperphosphatemia (Lacson, et al., 2009; Trivedi, et al., 2005) and anemia (Avram, et al., 2003; Lacson, et al., 2009; Locatelli, et al., 2004), but similar associations have not been found in the studies on ESRD patients with diabetes (Avram, et al., 2003; Foley, et al., 1997; Morioka, et al., 2001; Smavatkul, et al., 2007). In accordance with these results, low albumin (Coronel, et al., 2009; Foley, et al., 1997) and low predialysis phase creatinine (Morioka, et al., 2001) have been shown to correlate with worse survival in patients with diabetes on RRT, although also nonsignificant correlation between albumin and mortality (Hoher, et al., 2007) and better survival associating with higher glomerular filtration rate (Coronel, et al., 2009) have also been reported. High C-reactive protein as a marker of an ongoing inflammatory process is shown to associate with increased mortality among ESRD patients (Hoher, et al., 2003; Panichi, et al., 2008), which is also in line with our findings.

The prevalence of medication has not been studied previously during predialysis phase of kidney disease. However, studies among patients on RRT have reported 14–32% utilization of ACEIs, 31–70% of CCBs, 9–27% of beta-blockers, 10% of statins, and 13% of ARBs (Foley, et al., 2002; Griffith, et al., 2003; Ishani, et al., 2004; Lopes, et al., 2009). A markedly higher prevalence of medication was found here during predialysis phase. Reasons for this difference may include higher prevalence of comorbidities among ESRD patients with type 1 diabetes, earlier time period of these referred studies, and the common practice of discontinuing antihypertensive medication after RRT start.

Only few randomized trials have studied the effect of medication use on survival in patients with predialysis phase or end-stage renal disease. These studies have not been able to show significant effect on mortality with use of statins (Baigent, et al., 2011; Fellstrom, et al., 2009; Wanner, et al., 2005). Randomised studies have shown that ACEIs and ARBs are beneficial in diabetic nephropathy by reducing albuminuria and slowing down progression of renal disease, but they did not find any effect on survival, although follow-up times were short (Brenner, et al., 2001; Lewis, et al., 2001). Mortality has not decreased in randomized trials aiming for higher hemoglobin levels with use of erythropoietin in patients with chronic kidney disease (Besarab, et al., 1998; Pfeffer, et al., 2009). When patients with ESRD and chronic heart failure were treated in addition to standard therapy with carvedilol or telmisartan, two randomized trials showed significant mortality risk reduction (Cice, et al., 2003; Cice, et al., 2010). Recent meta-analysis reported that use of non-calcium-based phosphate binders was associated with lower mortality than use of calcium-based phosphate binders (Jamal, et al.,

2013). Taken together, evidence that medicine utilization would improve survival among patients with predialysis phase or end-stage renal disease is scarce.

A few large observational studies among ESRD patients have assessed associations between medicine utilization and survival. Better survival has been reported to associate with use of CCBs and not with beta-blockers (Griffith, et al., 2003; Ishani, et al., 2004; Kestenbaum, et al., 2002). However, a large study from the United States reported opposite results (Foley, et al., 2002). Use of statins or ARBs have also been reported to associate with better survival (Andreucci, et al., 2004; Ishani, et al., 2004; Lopes, et al., 2009). In hemodialysis patients low vitamin D (25-hydroxyvitamin D and 1,25-dihydroxyvitamin D) concentration is reported to associate with higher mortality (Wolf, et al., 2007) and activated vitamin D injections (calcitriol or paricalcitol) to associate with improved survival (Teng, et al., 2005). The findings reported here on vitamin D utilization and mortality after RRT start are in line with these results. Thus, the evidence of a beneficial effect of medication on mortality is limited and partly conflicting. One reason for these contradictory results may be the difference in the patient cohorts. The cause of renal disease and the number of comorbidities have a significant effect on mortality, and therefore the evaluation of correlation between medication and mortality is more reliable when assessed in more specifically defined patient groups.

CONCLUSIONS AND FUTURE PROSPECTS

In summary, this work has demonstrated that the survival of patients with type 1 diabetes on RRT in Finland has improved during the last three decades. This improvement appears to be the result of development in RRT and diabetes management in addition to advancement of healthcare in general. These patients have more comorbidities than other patients on RRT, and comorbidities are significant predictors of death. Biochemical variables can be used to evaluate the risk of death when initiating RRT, and especially hypoalbuminemia and low creatinine concentration at start of RRT predict mortality. Patients with type 1 diabetes use abundant medication during the predialysis phase of renal disease, and the use of medication appeared to keep patients on an equal survival level to patients not on the same medication.

Because these studies were observational and thus not ideal for assessing causal association between observed factors and survival, randomized trials are needed to confirm these findings. The results of these studies may be helpful when designing such trials.

According to these results, effort should be put into diagnosis, early treatment, and particularly prevention of comorbidities in patients with type 1 diabetes and nephropathy. Treatment of malnutrition, proteinuria, and hyperglycemia, and efficient dialysis therapy appear important in attempt to improve survival of these patients on RRT in the future.

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